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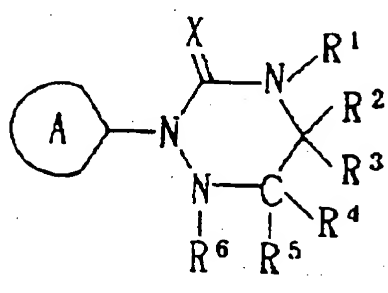
(71) Applicant: TAKEDA CHEMICAL INDUSTRIES, LTD.
1-1, Doshomachi 4-chome
Chuo-ku,
Osaka 541 (JP)

(72) Inventor: Miki, Hideki
23-14, Shinkofudai 2-chome,
Toyono-cho
Toyone-gun,
Osaka 563-01 (JP)
Inventor: Iwanaga, Koichi
201-1-5, Fushiodai 5-chome
Ikeda,
Osaka 563 (JP)
Inventor: Matsuno, Toshimi
14-9-1103, Niitaka 6-chome
Yodogawa-ku,
Osaka 532 (JP)

(74) Representative: Fürniss, Peter, Dr.
Kuhnen, Wacker & Partner
Alois-Steinecker-Strasse 22
D-85354 Freising (DE)

(54) Triazine derivative, production and use thereof.

(57) The present invention provides a novel triazine derivative of the formula



wherein ring A is an optionally substituted aromatic group which be;

X is an oxygen or sulfur atom;

R^1 and R^6 ar each a hydrogen atom or an optionally substitut d hydrocarbon residue or h terocyclic group which may bound through a het roatom;

R^2 and R^3 are each independently a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen or sulfur atom, or tak n together, r present =S;

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R^4 and R^5 are each independently a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen, nitrogen or sulfur atom;

R^1 and R^2, and R^5 and R^6, may each bind together to form a chemical bond; provided that where ring A is a phenyl group having at least a halogen atom in position-2 or 4 and X is an oxygen atom, R^4 and R^5 do not conjoinedly represent a chemical bond and an antiprotozoan composition containing the same or salt thereof.

Field of the Invention

The present invention relates to a novel triazine derivative or a salt thereof, and uses for them. More particularly, the invention relates to the novel triazine derivatives or a salt thereof, which is useful for controlling parasitic protozoa, particularly coccidia and the like, and an antiprotozoan composition comprising them.

Background of the Invention

Parasitic protozoa are parasites on a broad range of animals inclusive of mammals, birds, fishes and insects. The parasitic protozoa establish themselves in the internal organs or the external organs such as the skin and eye of the host animal. As such, these parasites give the hosts serious lesion and often infect the producing farmers of domestic animals, poultry and fish, causing great economic damage. Coccidiosis, which is one of the diseases causing the most serious economic damage to breeding, is mainly caused by several kinds of protozoa of the genus Eimeria, such as E. tenella, E. necatrix, E. acervulira, E. maxima, E. brunetti and E. mivati.

For example, E. tenella parasitizes the intestinal inner walls, such as that of the caecum, and often inflicts fatal damage on the host. Thus, the E. tenella infection produces several manifestations such as extensive erosion, inflammation and hemorrhage of the intestinal paries due to the development of the protozoa, caecal blood retention, and, hence, anaemia, retardation of growth or death of the host. Endoparastic protozoa are usually transmitted orally and as to coccidiosis in particular, even intensive disinfection with potassium dichromate solution fails to kill the oocysts. Moreover, since their life cycle is as short as about 7 days, one engaged in large-scale animal farming has to face the outbreak and spread of disease without an effective countermeasure.

As far as fishes are concerned, ectoparasitic protozoa are serious problems of concern. Their parasitization damages the host's skin and gills, weakens the resistance of the host fish to infections and may occasionally be fatal. In large-scale fish farming, parasitic protozoa spread among the whole fish population on a farm and the resulting economic loss is too large to be overlooked.

A similar situation prevails for insects. Taking bees as an example, parasitic protozoan represented by Nosema apis are doing a great deal of harm to apiculture all over the world. Nosema apis destroys the internal organs to debilitate the host bee, and the host with accordingly decreased resistance tends to succumb to various other diseases.

Several drugs against parasitic protozoa have been proposed but most of them are limited in the indication and spectrum of activity and even protozoa with acquired resistance to certain drugs are already known. Furthermore, the weak activity of these drugs requires massive doses so that none are satisfactory enough from both economic and ecological points of view. Therefore, development of drugs which can be used broadly with sufficient effectiveness for control of such parasites in animals, poultry, fishes and insects are awaited in earnest.

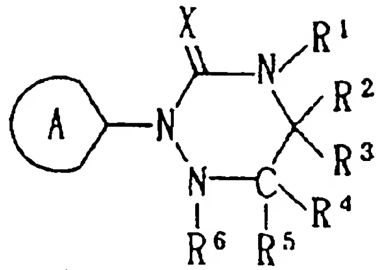
As such drugs, 2-phenyl-6-azauracil derivatives were found to have an anticoccidial activity [J. Med. Chem. 22, 1483 (1979)] and a variety of 6-azauracil derivatives were synthesized and tested. However, these compounds were found to be teratogenic and, therefore, could not find application in the field. As compounds which overcame the problems related to the teratogenicity, 1,2,4-triazinediones are in use in some European countries, Australia and Hungary or South Africa as anticoccidial drugs. However, since these compounds remain in the body in long time their use is critically restricted and even banned in several countries including Japan.

In view of above state of the art, the present inventors have researched and found that a series of novel triazine derivatives have excellent activity against parasitic protozoa. Further intensive research led them to the discovery that this series of derivatives is suited for the control of a broad spectrum of parasitic protozoa encountered in rearing and raising animals such as mammals, birds, fish and insects under the usual husbandry and breeding conditions, are of low toxicity to animals, and exhibit remarkably high antiprotozoal activity even against strains resistant to the drugs heretofor- available. This invention has been brought into b ing on the basis of the above findings.

The summary of the Invention

The present invention is direct d to:

(1) a triazine derivative of the formula



wherein ring A is an optionally substituted aromatic group;
X is an oxygen or sulfur atom;
R^1 and R^6 are each independently a hydrogen atom or an optionally substituted hydrocarbon residue or heterocyclic group which may bound through a heteroatom;
R^2 and R^3 are each independently a hydrogen atom, a halogen atom, or a group bonding through a carbon, oxygen or sulfur atom, or, taken together, represent =S;
R^4 and R^5 are each independently a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen, nitrogen or sulfur atom;
R^1 and R^2, and R^5 and R^6 taken together may form a chemical bond; provided that where ring A is a phenyl group having at least a halogen atom in positions 2 or 4 and X is an oxygen atom, R^5 and R^6 do not bind together to form a chemical bond or salt thereof,
(2) an antiprotozoan composition comprising an effective amount of the triazine derivative or salt mentioned above (1) and a physiologically acceptable carrier, excipient or diluent. (3) a feed additive which comprises the triazine derivatives or a salt thereof as mentioned above, and (4) a method of rearing and breeding animals which comprises administering an effective amount of the triazine derivatives or a salt mentioned above. The present invention also relates to (5) a method of preparing the triazine derivatives, or the antiprotozoal composition.

Referring to the above formula, the optionally substituted aromatic group, ring A, includes 5 to 6-membered homo- or hetero-aromatic groups which may have one or more substituents.

The carbocycle of said optionally substituted homoaromatic group may for example be benzene.

The heteroaromatic group includes 5- or 6-membered unsaturated heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, for example 5-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, such as 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4-or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, etc., and 6-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, such as 2-, 3- or 4-pyridyl, N-oxide-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxide-2-, 4- or 5-pyrimidinyl, oxoimidazinyl, dioxotriazinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, triazinyl, oxotriazinyl, 3-or 4-pyridazinyl, pyrazinyl, N-oxide-3- or 4-pyridazinyl, etc. Among them, 6-membered heterocyclic groups having one hetero-atom as a ring member are preferred and nitrogen-containing heterocyclic groups are particularly desirable.

Such a homo- or hetero-aromatic group may be substituted, in 1 to 5 or preferably 1 to 3 substitutable positions, by the following substituent groups, among others;
(1) C_{1-4} alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.
(2) C_{2-4} alkenyl, e.g. vinyl, 1-methylvinyl, 1-propenyl, allyl, etc.
(3) C_{2-4} alkinyl, e.g. ethinyl, 1-propinyl, propargyl, etc.
(4) C_{3-6} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.
(5) C_{5-7} cycloalkenyl, e.g. cyclopentenyl, cyclohexenyl, etc.
(6) C_{7-11} aralkyl, e.g. benzyl, α-methylbenzyl, phenethyl, etc.
(7) phenyl
(8) C_{1-6} alkoxy, e.g. m thoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, etc.
(9) phenoxy
(10) C_{1-6} alkanoyl, e.g. formyl, acetyl, propionyl, n-butyryl, iso-butyryl, tc.

(11) benzoyl
(12) C_{1-6} alkanoyloxy, e.g. formyloxy, acetyloxy, propionyloxy, n-butyryloxy, iso-butyryloxy, etc. and benzoyloxy
(13) carboxyl
(14) C_{2-7} alkoxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.
(15) carbamoyl
(16) N-mono-C_{1-4} alkylcarbamoyl, e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, etc.
(17) N-di-C_{1-4} alkylcarbamoyl, e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-dibutylcarbamoyl, etc.
(18) cycloaminocarbonyl, e.g. 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl, morpholinocarbonyl, etc.
(19) halogens, e.g. F, Cl, Br, I,etc.
(20) mono-, di- or tri-halo-C_{1-4} alkyl, e.g. chloromethyl, dichloromethyl, trifluoromethyl, trifluoroethyl, etc.
(21) oxo
(22) amidino
(23) imino
(24) optionally protected amino (the protected group for amino group is defined below)
(25) mono-C_{1-4} alkylamino, e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.
(26) di-C_{1-4} alkylamino, e.g. dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, etc.
(27) 3- to 6-membered cycloamino which may contain 1 to 3 hetero-atoms selected from among oxygen, sulfur, nitrogen, etc. in addition to at least one carbon atom and one nitrogen atom, such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.
(28) C_{1-6} alkanamido such as formamido, acetamido, trifluoroacetamido, propionamido, butyrylamido, isobutyrylamido, etc.
(29) benzamido
(30) carbamoylamino
(31) N-C_{1-4} alkylcarbamoylamino, e.g. N-methylcarbamoylamino, N-ethylcarbamoylamino, N-propylcarbamoylamino, N-isopropylcarbamoylamino, N-butylcarbamoylamino, etc.
(32) N-N-di-C_{1-4} alkylcarbamoylamino, e.g. N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino, N,N-dibutylcarbamoylamino, etc.
(33) C_{1-3} alkylenedioxy, e.g. methylenedioxy, ethylenedioxy, etc.
(34) $-B(OH)_2$
(35) hydroxy
(36) epoxy (-O-)
(37) nitro
(38) cyano
(39) mercapto
(40) sulfo
(41) sulfino
(42) phosphono
(43) dihydroxypolyol
(44) sulfamoyl
(45) C_{1-6} monoalkylsulfamoyl, e.g. N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.
(46) di-C_{1-4} alkylsulfamoyl, e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.
(47) C_{1-6} alkylthio, e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio, tert-butylthio, etc.
(48) phenylthio
(49) C_{1-6} alkylsulfinyl, e.g. methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.
(50) phenylsulfinyl
(51) C_{1-6} alkylsulfonyl, e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, tc.
(52) phenylsulfonyl and

(53) 5- or 6-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, which may be bound through a one or two atom chain containing oxygen, sulfur, nitrogen, carbon or the like, for example 2- or 3-thi nyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxide-2-, 3-or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxide-2-, 4-or 5-pyrimidinyl, oxoimidazinyl, dioxotriazinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, triazinyl, oxotriazinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxide-3- or 4-pyridazinyl, and so on.

Of the above-mentioned groups, any group having a carbon chain of 2 or more C atoms or a cyclic group may be further substituted, in 1 or 2 substitutable positions, by such substituent groups as

(a) halogens, e.g. Cl, F, etc.

(b) hydroxy,

(c) oxo,

(d) C_{1-4} alkoxy, e.g. methoxy, ethoxy, etc.

(e) di-C_{1-4} alkylamino, e.g. dimethylamino, diethylamino, etc.

(f) halo-C_{1-4} alkyl, e.g. chloromethyl, trifluoromethyl, trifluoroethyl, etc.

(g) C_{1-4} acyl, e.g. formyl, acetyl, etc.

(h) hydroxy-C_{1-4} alkyl, e.g. hydroxymethyl, 2-hydroxyethyl, etc.

(i) C_{1-4} alkoxy-C_{1-4} alkyl, e.g. methoxymethyl, 2-ethoxyethyl etc.

(j) cyano

(k) thioxo and

(l) C_{1-4} alkylthio, e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio, t-butylthio and so on.

Further, when the substitution exists on two ring-forming atoms adjacent to each other, they may bind together to form a ring. The condensed ring thus formed is a 8 to 10 membered bicyclic ring which includes bicyclic aryl group such as 1- or 2-pentalenyl, 1- or 2- indenyl (1H- or 2H- indenyl) or 1-or 2-naphthylyl, and bicyclic heterocyclic ring containing 1 to 4 hetero atom selected from among oxygen, sulfur, or nitrogen in addition to at least one carbon atom, such as indolyl, isoindolyl, benzofuryl, benzothiophenyl, benzothiazolyl, benzoxazolyl, tetrazolo[1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolynyl, quinoxalinyl, indolidinyl, quinolidinyl, 1,8-naphthylidinyl, purinyl, putheridinyl, dibenzofuranyl, chromanyl, benzoxazinyl or like.

Among the above exemplified substituents, halogen atom, optionally substituted alkyl, especially C_{1-4} alkyl group, haloalkyl group or optionally substituted aralkyl, especially phenyl C_{1-4} alkyl group, a phenyl or heterocyclic group which may be bound through an atomic chain of 1 or 2 atoms such as phenoxy, phenylthio, benzoyl, benzoyloxy, phenylsulfonyl, benzomide and heterocyclic group optionally bound through an atomic chain of 1 or 2 atoms are preferable.

In regard to substitution topology, the benzene ring, for instance, may preferably be substituted in position 3 and/or 5, more preferably be substituted in position 4 in addition to the substitution in 3 and/or 5 but these are not exclusive choices, of course.

X represents an oxygen or sulfur atom and is preferably an oxygen atom.

Where R^1 and R^6 are the optionally substituted hydrocarbon residues each of which may be bound through a hetero-atom, the particular hydrocarbon residue includes, among others, C_{1-15} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, etc., C_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc., C_{2-10} alkenyl such as vinyl, allyl, 2-methylallyl, 2-butenyl, 3-butenyl, 3-octenyl, etc., C_{2-10} alkinyl such as ethinyl, 2-propinyl, 3-hexinyl, etc., C_{3-10} cycloalkenyl such as cyclopropenyl, cyclopentenyl, cyclohexenyl, etc., C_{6-14} aryl such as phenyl, naphthyl, etc., C_{7-16} aralkyl such as benzyl, phenylethyl, etc. Among them alkyl, aryl and aralkyl group are preferable. Hydrocarbon residues having 1 to 7 carbon atoms are also preferable. Any of such hydrocarbon groups may have 1 to 5 substituent groups in substitutable positions as selected from among

(1) nitro

(2) hydroxy

(3) oxo

(4) thioxo

(5) cyano

(6) carbamoyl

(7) carboxyl
(8) C_{1-4} alkoxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, etc.
(9) sulfo
(10) halogens, e.g. F, Cl, Br, I, etc.
(11) C_{1-4} lower alkoxy, e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy, t-butoxy, etc.
(12) phenoxy
(13) halophenoxy, e.g. o-, m- or p-chlorophenoxy, o-, m- or p-bromophenoxy, etc.
(14) C_{1-4} lower alkylthio, e.g. methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio, etc.
(15) phenylthio
(16) C_{1-4} lower alkylsulfinyl, e.g. methylsulfinyl, ethylsulfinyl, etc.
(17) C_{1-4} lower alkylsulfonyl, e.g. methylsulfonyl, ethylsulfonyl, etc.
(18) amino
(19) C_{1-6} lower acylamino, e.g. acetylamino, propionylamino, etc.
(20) mono- or di-C_{1-4} alkylamino, e.g. methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, dimethylamino, diethylamino, etc.
(21) C_{1-4} lower acyl, e.g. formyl, acetyl, etc.
(22) benzoyl
(23) 5- or 6-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, such as 2- or 3-thienyl, 2- or 3-furyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 1,2,3- or 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidyl, 3- or 4-pyridazinyl, quinolyl, isoquinolyl, indolyl, etc. which may be substituted by 1 to 4 substituents selected from among (a) halogens such as Br, Cl, F, etc., (b) C_{1-4} lower alkyl such as methyl, ethyl, propyl, isopropyl, etc. and (c) halophenoxy such as o-, m- or p-chlorophenoxy, o-, m-or p-bromophenoxy, etc.
(24) C_{1-10} haloalkyl, e.g. difluoromethyl, trifluoromethyl, trifluoroethyl, trichloroethyl, etc. Furthermore, where the hydrocarbon residue is cycloalkyl, cycloalkenyl, aryl or aralkyl, it may have 1 to 4 C_{1-4} lower alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, etc as substituents.

Among the exemplified hydrocarbon residues, alky, aryl and aralkyl groups are preferable. The hydrocarbon residue having 1 to 8 is also preferable.

The acyl group of the hydrocarbon residue represented by R^1 or R^6 includes a group having a general formula of -COR^a, -CONHR^a, -CSR^a or -CSNHR^a wherein R^a represents hydrogen or the above exemplified hydrocarbon group represented by R^1 or R^6. The hydrocarbon group of R^a may have 1 to 2 substituents in substitutable position as selected from among the above exemplified group under (1) through (23). Among them, C_{1-7} acyl group wherein R^a is C_{1-6} hydrocarbon group such as C_{1-6} alkyl group (e.g. methyl, ethyl etc.), C_{2-6} alkenyl group (e.g. vinyl), C_{2-6} alkynyl group (e.g. ethynyl), C_{3-6} cycloalkyl group (e.g. cyclohexyl), C_{3-6} cycloalkenyl group (e.g. cyclohexenyl) or phenyl is preferable.

The oxycarbonyl group of the hydrocarbon residue represented by R^1 or R^6 includes a group having a general formula of -COOR^a wherein R^a is the same meaning definded above. The hydrocarbon group of R^a may have 1 to 2 substituents in substitutable position as selected from among the above exemplified group under (1) through (23). Preferred, among the alkoxycarbonyl group, is the group wherein R^a is C_{1-6} hydrocarbon group such as C_{1-6} alkyl group (e.g. methyl, ethyl etc.), C_{2-6} alkenyl gorup (e.g. vinyl), C_{2-6} alkynyl group (e.g. ethynyl), C_{3-6} cycloalkyl group (e.g. cyclohexyl), C_{3-6} cycloalkenyl group (e.g. cyclohexenyl) or phenyl.

The optionally substituted heterocyclic group which may be bound through a hetero-atom includes, among others, 5- to 8-membered heterocyclic groups or condensed heterocyclic groups derived therefrom containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, for example 5-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, such as 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4-or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, etc., 6-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among oxyg n, sulfur, nitrogen and the like in addition to at least one carbon atom, such as N-oxide-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxide-2-, 4- or 5-pyrimidinyl, thiomorpholinyl, morpholinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, piperidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, piperazinyl, triazinyl, oxotriazinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxide-

3-or 4-pyridazinyl, etc. and bicyclic or tricyclic condensed heterocyclic groups containing 1 to 4 heteroatoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, such as benzofuryl, benzothiazolyl, benzoxazolyl, tetrazolo[1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolynyl, quinoxalinyl, indolidinyl, quinolidinyl, 1,8-naphthylidinyl, purinyl, putheridinyl, dibenzofuranyl, carbazolyl, acrylidinyl, phenanthrydinyl, chromanyl, benzoxazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, etc. Among them uncondensed heterocyclic rings, especially 5- or 6-membered rings, are preferable. Any of such heterocyclic groups may have 1 to 5 substituent groups selected from among

(1) C_{1-4} alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, ter-butyl, etc.
(2) C_{2-4} alkenyl, e.g vinyl, 1-methylvinyl, 1-propenyl, allyl, etc.
(3) C_{2-4} alkinyl, e.g. ethinyl, 1-propinyl, propargyl, etc.
(4) C_{3-6} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.
(5) C_{5-7} cycloalkenyl, e.g. cyclopentenyl, cyclohexenyl, etc.
(6) C_{7-11} aralkyl, e.g. benzyl, α-methylbenzyl, phenethyl, etc.
(7) phenyl
(8) C_{1-6} alkoxy, e.g. methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, etc.
(9) phenoxy
(10) C_{1-6} alkanoyl, e.g. formyl, acetyl, propionyl, n-butyryl, iso-butyryl, etc.
(11) benzoyl
(12) C_{1-6} alkanoyloxy, e.g. formyloxy, acetyloxy, propionyloxy, n-butyryloxy, iso-butyryloxy, etc., benzoyloxy
(13) carboxyl
(14) C_{2-7} alkoxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.
(15) carbamoyl
(16) N-mono-C_{1-4} alkylcarbamoyl, e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, etc.
(17) N,N-di-C_{1-4} alkylcarbamoyl, e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-dibutylcarbamoyl, etc.
(18) cycloaminocarbonyl, e.g. 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl, morpholinocarbonyl, etc.
(19) halogens, e.g. F, Cl, Br, I, etc.
(20) mono-, di- or tri-halo-C_{1-4} alkyl, e.g. chloromethyl, dichloromethyl, trifluoromethyl, trifluoroethyl, etc.
(21) oxo
(22) amidino
(23) imino
(24) amino
(25) mono-C_{1-4} alkylamino, e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.
(26) di-C_{1-4} alkylamino, e.g. dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, etc.
(27) 3- to 6-membered cycloamino containing 1 to 3 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom and one nitrogen atom, such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.
(28) C_{1-6} alkanoylamido, e.g. formamido, acetamido, trifluoroacetamido, propionylamido, butyrylamido, isobutyrylamido, etc.
(29) benzamido
(30) carbamoylamino
(31) N-C_{1-4} alkylcarbamoylamino, e.g. N-methylcarbamoylamino, N-ethylcarbamoylamino, N-propylcarbamoylamino, N-isopropylcarbamoylamino, N-butylcarbamoylamino, etc.
(32) N,N-di-C_{1-4} alkylcarbamoylamino, e.g. N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino, N,N-dibutylcarbamoylamino, etc.
(33) C_{1-3} alkylen dioxy, .g. m thylenedioxy, ethylenedioxy, etc.
(34) $-B(OH)_2$
(35) hydroxy
(36) epoxy (-O-)
(37) nitro

(38) cyano
(39) mercapto
(40) sulfo
(41) sulfino
(42) phosphono
(43) dihydroxypolyol
(44) sulfamoyl
(45) C_{1-6} monoalkylsulfamoyl, e.g. N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.
(46) di-C_{1-4} alkylsulfamoyl, e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.
(47) C_{1-6} alkylthio, e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio, tert-butylthio, etc.
(48) phenylthio
(49) C_{1-6} alkylsulfinyl, e.g. methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.
(50) phenylsulfinyl
(51) C_{1-6} alkylsulfonyl, e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc. and
(52) phenylsulfonyl.

The above optionally substituted hydrocarbon residue or heterocyclic group which may be bound through a hetero-atom is, for example, the nitrogen atom of amino, substituted amino (e.g. amino C_{1-4} alkylamino, hydroxyamino, etc.), or hydrazino, the sulfur atom of thiocarbonyl or sulfino, or an oxygen atom.

Preferred, among the above-mentioned optionally substituted hydrocarbon residues and heterocyclic groups which may be bound through a hetero-atom, are optionally substituted alkyl, aryl, aralkyl and optionally substituted nitrogen-containing heterocyclic groups which may be bound through a hetero-atom and more preferred are optionally substituted C_{1-4} alky group. C_{1-7} acyl group and C_{1-7} oxycarbonyl group are also preferable.

The group bound through a carbon, oxygen or sulfur atom, represented by R^2 and R^3, includes, among others,

(1) cyano
(2) carboxy
(3) carbamoyl
(4) mercapto
(5) hydroxy
(6) C_{1-4} alkyl, e.g. methyl, ethyl, propyl, iso-propyl, etc.
(7) C_{1-6} alkylthio, e.g. methylthio, etc.
(8) C_{7-11} alalkylthio, e.g. benzylthio, etc.
(9) C_{2-4} alkenyl, e.g vinyl, 1-methylvinyl, 1-propenyl, allyl, allenyl, etc.
(10) C_{2-4} alkinyl, e.g. ethinyl, 1-propinyl, propargyl, etc.
(11) C_{1-6} alkoxy e.g. methoxy, etc.
(12) C_{3-6} cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl, etc.
(13) C_{6-10} aryl, e.g. phenyl, naphthyl, etc, or
(14) 5- to 7-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among nitrogen, sulfur, oxygen and the like in addition to at least one carbon atom, such as pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, dioxolanyl, piperidino, morpholino, N-methylpiperazinyl, N-ethylpiperazinyl, dioxanyl, etc. Among the above-mentioned groups, the groups mentioned under (6) through (14) may have 1 or 2 substituent groups in substitutable positions as selected from among

(a) halogens, e.g. Cl, F, etc.
(b) hydroxy
(c) oxo
(d) C_{1-4} alkoxy, e.g. methoxy, ethoxy, etc.
(e) di-C_{1-4} alkylamino, e.g. dimethylamino, diethylamino, etc.
(f) halo-C_{1-4} alkyl, .g. chlorom thyl, trifluorom thyl, trifluoroethyl, etc.
(g) C_{1-4} acyl, e.g. formyl, acetyl, etc.
(h) hydroxy-C_{1-4} alkyl, e.g. hydroxymethyl, 2-hydroxyethyl, etc.,
(i) C_{1-4} alkoxy-C_{1-4} alkyl, e.g. methoxym thyl, 2-ethoxyethyl, etc.
(j) thioxo,
(k) sulfide,

(l) C_{3-6} cyloalkyl, .g. cyclopropyl, etc., and

(m) mercaplo

Th halogen atom may for example be chlorine, bromine, fluorine or iodine.

Preferred, among the above, are halogen atoms and optionally substituted alkyl or aryl groups which may be bound through an oxygen or sulfur atom. Among alkyl groups a low alkyl group of 1 to 4 carbon atoms is preferable and phenyl is a preferable aryl group.

The group bound through a carbon, nitrogen, oxygen or sulfur atom, R^4 and R^5, includes

(1) cyano

(2) carboxy

(3) carbamoyl

(4) amino

(5) nitro

(6) hydroxy

(7) mercapto

(8) C_{1-4} alkyl, e.g. methyl, ethyl, propyl, iso-propyl, etc.

(9) C_{2-4} alkenyl, e.g. vinyl, 1-methylvinyl, 1-propenyl, allyl, allenyl, etc.

(10) C_{2-4} alkinyl, e.g. ethinyl, 1-propinyl, propargyl, etc.

(11) C_{3-6} cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl, etc.

(12) C_{6-10} aryl, e.g. phenyl, naphthyl, etc. or

(13) 5- to 7-membered heterocyclic groups containing 1 to 4 hetero-atoms selected from among nitrogen, sulfur, oxygen and the like in addition to at least one carbon atom, such as pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, dioxolanyl, piperidino, morpholino, N-methylpiperazinyl, N-ethylpiperazinyl, dioxanyl, etc. Among these groups, the groups mentioned under (8) through (13) may have 1 or 2 substituent groups in substitutable positions as selected from among

(a) halogens, e.g. Cl, F, etc.

(b) hydroxy

(c) oxo

(d) C_{1-4} alkoxy, e.g. methoxy, ethoxy, etc

(e) di-C_{1-4} alkylamino, e.g. dimethylamino, diethylamino, etc.

(f) halo-C_{1-4} alkyl, e.g. chloromethyl, trifluoromethyl, trifluoroethyl, etc.

(g) C_{1-4} acyl, e.g. formyl, acetyl, etc.

(h) hydroxy-C_{1-4} alkyl, e.g. hydroxymethyl, 2-hydroxyethyl, etc., and

(i) C_{1-4} alkoxy-C_{1-4} alkyl, e.g. methoxymethyl, 2-ethoxyethyl, etc.

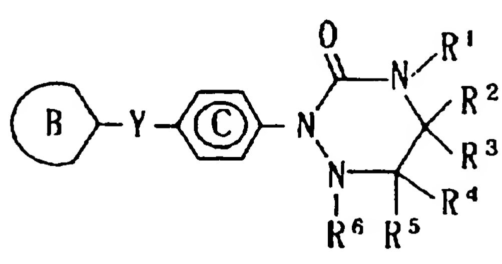
The halogen may for example be chlorine, bromine, fluorine or iodine.

Preferred, among the above, are halogens and alkyl or aryl groups optionally substituted and/or each bonding through a nitrogen, oxygen or sulfur atom.

R^1 and R^2, or R^5 and R^6, may each bind together to form a chemical bond, that is to say a double bond between the carbon atom at 5-position and nitrogen atom at 4-position or between the carbon atom at 6-position and nitrogen atom at 1-position of the triazine ring. The double bond between 4- and 5-positions and that between 1- and 6-positions may exist concurrently but it is preferable that only one of them exists and is more preferable that a double bond be present between the 1- and 6-positions.

Where the triazine ring is tautomeric, the respective tautomers are also subsumed in the concept of triazine derivative of this invention.

Among the triazine derivatives of the present invention the compound of the following formula or salt thereof are preferable:



wherein R^1, R^2, R^3, R^4, R^5 and R^6 are the same meanings defined above, ring B is an optionally substituted 5- or 6-membered cyclic group which may contains hetero atoms, ring C is an optionally substituted phenylen group, Y is a chemical bond, -O-, -$S(O)_m$- or an optionally protected amino or an optionally substituted lower hydrocarbon and m is 0, 1 or 2.

Optionally substituted 5- or 6-membered cyclic group represented by ring B includes carbon rings such as cycloalkyl, such as cyclopentyl or cyclohexyl, etc., cycloalkenyl, such as 1-, 2- or 3- cyclopentenyl, 1-, 2- or 3- cyclohexenyl, etc., phenyl or heteroaromatic groups containing 1 to 4 hetero-atoms selected from among oxygen, sulfur, nitrogen and the like in addition to at least one carbon atom, for example 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4-or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, etc., N-oxide-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxide-2-, 4- or 5-pyrimidinyl, oxoimidazinyl, dioxotriazinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, triazinyl, oxotriazinyl; 3- or 4-pyridazinyl, pyrazinyl, N-oxide-3- or 4-pyridazinyl, etc. Among them, 6-membered cyclic groups, especially phenyl is preferable and 6-membered nitrogen-containing heterocyclic groups are particularly desirable when ring B is a heterocyclic group.

Such a cyclic group may be substituted, in 1 to 5 or preferably 1 to 3 substitutable positions, by the following substituent groups, among others:

(1) C_{1-4} alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.
(2) C_{1-4} lower alkoxy, e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutosy, s-butoxy, t-butoxy, etc.
(3) carboxy
(4) carbamoyl
(5) halogens, e.g. F, Cl, Br, I, etc.
(6) mono-, di- or tri halo-C_{1-4} alkyl e.g. chloromethyl, dichloromethyl, trifluoromethyl, trifluoroethyl, etc.
(7) amino
(8) -$B(OH)_2$
(9) hydroxy
(10) nitro
(11) cyano
(12) mercapto
(13) sulfo
(14) sulfino
(15) phospho and
(16) C_{1-4} acyl e.g. folmyl acetyl etc.

Halogen atom or alkyl or haloalkyl group is preferable.

When the substitutions exist on two ring-forming atoms adjacent to each other, they may bind together to form a ring which is condensed with the ring B.

The optionally substituted phenylene group represented by the ring C may be substituted by 1 to 4 preferably 1 to 2, substituents selected from those of the ring A. Among them, a halogen atom, alkyl, alkoxy or haloalkyl group is desirable.

The lower hydrocarbon residue represented by Y includes a hydrocarbon group of 1 to 6 carbon atoms, for example C_{1-4} alkylene such as methylene, ethylene, propylene, trimethylene, tetramethylene etc, C_{2-6} alkenylene such as vinylene, propenylene, 1- or 2-butenylene, butadienylene etc. or C_{2-6} alkylydene such as ethylydene, propilydene buthylydene etc. These lower hydrocarbon groups are substituted with 1 to 4 substituents selected from .

(1) halogens, e.g. Cl, F, etc.
(2) hydroxy,
(3) oxo,
(4) cyano,
(5) C_{1-4} alkoxy, e.g. methoxy, ethoxy, etc.
(6) mono- or di-C_{1-4} alkylamino, e.g. methylamino, ethyklamino, propylamino, dimethylamino, diethylamino, dipropylamino, etc.
(7) halo-C_{1-4} alkyl, .g. fluoromethyl, fluo thyl, chlorom thyl, chloroethyl, bromomethyl, bromoethyl, trifluoromethyl, trifluoroethyl, chloropropyl, tc.
(8) C_{1-4} acyl, e.g. formyl, acetyl, propyonyl, etc.
(9) hydroxy-C_{1-4} alkyl, e.g. hydroxymethyl, hydroxyethyl, 2-hydroxyethyl, hydroxypropyl, etc.

(10) C_{1-4} alkoxy-C_{1-4} alkyl, e.g. m thoxymethyl, 2-ethoxyethyl, etc.
(11) C_{1-4} alkoxy-carbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, n-butoxycarbonyl, tert-butoxycarbonyl etc.
(12) thioxo and
(13) C_{1-4} alkylthio, e.g. methylthio, ethylthio, propylthio, isopropylthio, buthylthio, isobuthylthio, sec-buthylthio, tert-buthylthio etc. and so on.

Among them, a hydrocarbon group having 1 to 2 carbon atom in a straight chain which links the rings B and C such as optionally substituted methylene, ethylene, vinylene and ethynylene is preferable. Further, a C_{1-3} alkylene, C_{2-4} alkylene or C_{2-4} alkenylidene group which may optionally be substituted with 1 to 2 of the above mentioned substituents is most preferable.

For example, such a preferable embodiment includes methylene group optionally substituted with chloro, fluoro, methyl, monofluoromethyl, monochloromethyl, trifluoromethyl, hydroxy, carboxy, oxo (to a carbonyl group), thioxo (to a thiocarbonyl group), methoxycarbonyl, ethoxycarbonyl, cyano or the like, ethylene group optionally substituted, at position 1 or 2 independently, with chloro, fluoro, methyl, monofluoromethyl, monochloromethyl, trifluoromethyl, hydroxy, carboxy, cyano or like, propylen group optionally substituted, at position 1, 2, or 3 independently, with chloro, fluoro, methyl, monofluoromethyl, monochloromethyl, trifluoromethyl, hydroxy carboxy, oxo (to form e.g. ethylidenecarbonyl, acetylethylene etc.), methoxy, ethoxy, methylthio, ethylthio, dimethylamino, diethylamino or the like, C_{2-4} alkenylen group optionally substituted with chloro, fluoro methyl, monofluoromethyl, monochloromethyl, hydroxy, carboxy, cyano or the like independently on any substituted position, and C_{2-4} alkylidene group optionally substituted with chloro, fluoro, oxo (to form e.g. formylmethylene, acetylmethylene, methylcarbonyl-methylene etc, hydroxy, methoxy, ethoxy, methylthio, dimethylamino, diethylamino or the like.

In the optionally protected the amino of Y, amino group may be protected with a group selected from
(1) formyl
(2) C_{1-6} alkyl-carbonyl, e.g. acetyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl which may substituted with halogen atoms, e.g. Cl, Br, F etc.
(3) C_{6-10} aryl-carbonyl, e.g. phenylcarbonyl which may substituted with 1 to 3 halogen atom, e.g. Cl, Br, F etc, C_{1-6} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl etc. or nitro group
(4) C_{1-6} alkyloxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl which may substituted with 1 to 3 halogen atom, e.g. Cl, Br, F etc, C_{1-6} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl etc. or nitro group
(5) C_{6-10} aryloxycarbony, e.g. phenoxycarbony which may substituted with 1 to 3 halogen atom, e.g. Cl, Br, F etc. C_{1-6} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl etc. or nitro group
(6) C_{7-12} aralkyl-carbonyl, e.g. benzylcarbonyl, phenylethylcarbonyl which may substituted with 1 to 3 halogen atom, e.g. Cl, Br, F etc, C_{1-6} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl etc. or nitro group
(7) trityl which may substituted with 1 to 3 halogen atom, e.g. Cl, Br, F etc, C_{1-6} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl etc. or nitro group and
(8) phthaloyl which may substituted with 1 to 3 halogen atom, e.g. Cl, Br, F etc, C_{1-6} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl etc. or nitro group or the like. However, any group may be used as long as it can be re-converted to amino chemically in the synthesis rout using a general technique of organic chemistry or under physiological conditions (for example by enzymatic lysis or metabolism).

Among the divalent groups represented by Y, -O-, - S- or optionally substituted C_{1-6} bivalent hydrocarbon group, especially optionally substituted C_{1-4} alkylen or C_{2-4} alkylydene group is preferable.

In the above formula, prefered embodiments of R^1 and R^6 are each hydrogen atom or an optionally substituted hydrocarbon residue; especially alkyl, aryl or aralkyl group, which may be bound through a hetero atom.

Further, hydrogen, C_{1-7} acyl group (e.g. acetyl, benzyl etc.), C_{1-7} oxycarbonyl group (e.g. methoxycarbonyl, hydroxy carbonyl etc.) or an optionally substituted alkyl such as C_{1-4} alkyl, mono-, di- or trihalo-C_{1-4} alkyl, C_{1-4} alkylcarbonyl or the like is more preferred as R^1.

In the above formula, R^2 and R^3 are preferably selected each from among hydrogen atom, halogen atom and an optionally substituted alkyl such as C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, mono-, di- or trihalo- C_{1-4} or lik , aryl such as phenyl, phenoxy, phenylthio, mono-, di- or tri- halophenyl or aralkyl group such as benzyl, benzylthio or the like, or may b taken together to form =S, more pref rably s lected each from among hydrogen atom, halogen atom and an optionally substitut d alkyl group. Furth r, at least either,

especially both of R^2 and R^3 may preferably be a hydrogen atom.

In the above formula, R^4 and R^5 are preferably selected each from among, hydrogen atom, halogen atom and an optionally substituted alkyl or aryl group, more preferably selected from hydrogen or an optionally substituted C_{1-4} alkyl group. Further, at least either, especially both, of R^4 and R^5 may preferably be a hydrogen atom.

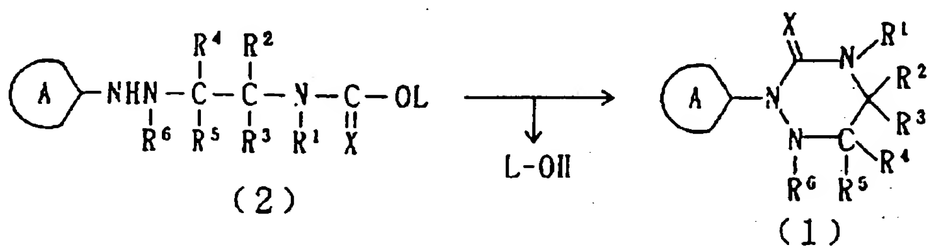
R^6 are preferred to be hydrogen or an optionally substituted C_{1-4} alkyl group such as C_{1-4} alkyl, mono-, di- or trihalo- C_{1-4} alkyl, C_{1-4} acyl, C_{1-4} alkylcarbony or the like.

The compounds in which R^1 and R^2 and/or R^5 and R^6 bind together to form a chemical bond are also desired.

The salt of a triazine derivative according to this invention is preferably a salt physiologically acceptable for animals and as such includes salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium etc., salts with inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, etc., and salts with organic acids such as acetic acid, succinic acid and so on.

The triazine derivative of this invention can be produced by, inter alia, the following reaction routes.

Reaction a)

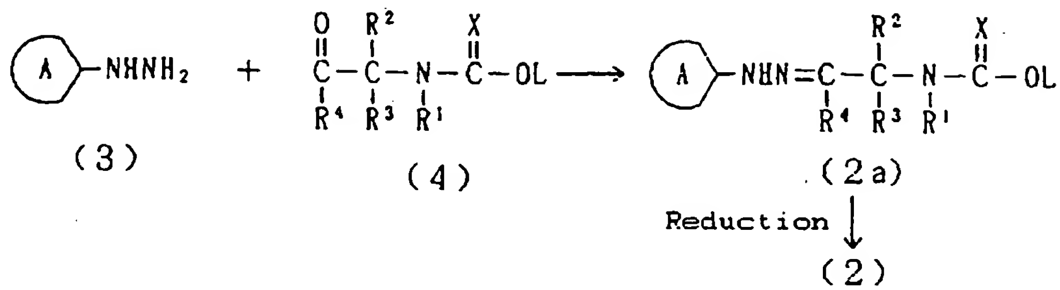


wherein ring A, X, R^1, R^2, R^3, R^4, R^5 and R^6 have the meanings defined hereinbefore; L represents hydrogen or an alkyl or aryl group.

The above reaction a) is directed to cyclization of hydrazine derivative (2) to a compound of general formula (1).

This reaction is generally conducted in an inert solvent or in the absence of a solvent, optionally in the presence of a Lewis acid or a Lewis base. The reaction temperature is generally about 60 to about 200 °C and preferably about 100 to about 160 °C. For this reaction, virtually any inert organic solvent can be employed. Thus, it may can be any of the reaction solvents which are generally used in organic chemistry, for example, benzene, ligroin, benzine, toluene, xylene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, ethers (e.g. dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphorotriamide, etc.), N-methylpyrrolidone, dimethylsulfoxide, tetramethylenesulfone, mercaptoacetic acid, pyridine, and so on. This reaction may be carried out while the byproduct such as alcohol or water is removed.

Reaction b)



wherein ring A, R^1 - R^4, L and X have the meanings defined hereinbefore.

The above reaction b) comprises reacting hydrazine (3) with a carbomic acid derivative (4) to give a hydrozone derivative (2a) followed by reduction to provide a hydrazine derivative (2).

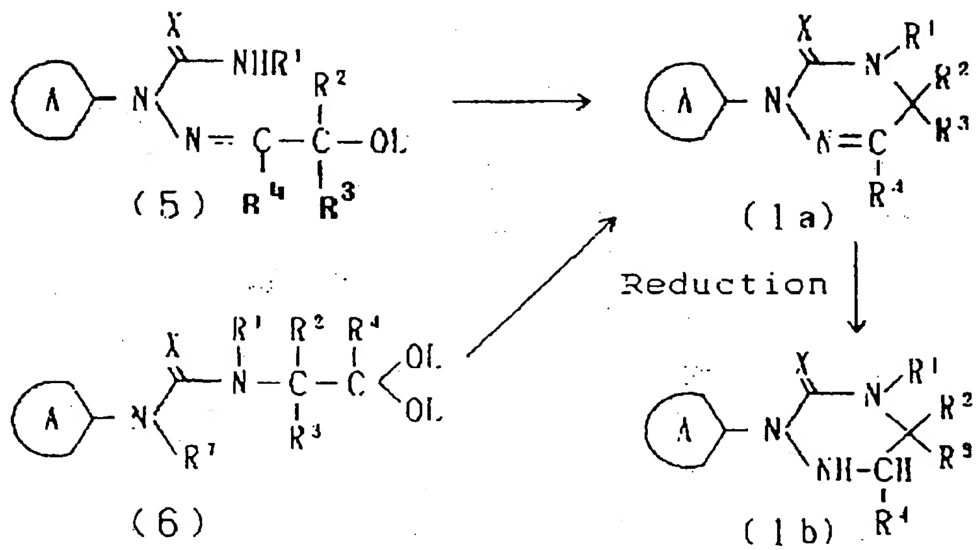
The compound (2a) obtained by reacting compound (3) with compound (4) in an inert organic solvent is then reduced in the conventional manner. The inert organic solvent that can be used includes, among others, hydrocarbons (e.g. nonane, decane, dodecane, xylene, toluene, benzene, etc.), halogenated hydrocarbons (e.g. chloroform, dichloromethane, carbone tetrachloride, chlorobenzene, dichloroethane, etc.), alcohols (e.g. diethylene glycol etc.), ethers (e.g. diethylene glycol monobutyl ether, diethylene glycol dibutyl ether, etc.), dioxane, tetrahydrofuran, dimethylformamide, sulfoxides and sulfones such as dimethyl sulfoxide, tetramethylenesulfone and so on. This reaction can also be conducted in the presence of a Lewis acid or a dehydrating agent (e.g. dicyclohexylcarbodiimide, carbonyldiimidazole, etc.).

This reaction can be carried out generally at a temperature within the range of about -10°C to about 150°C. In particular, the temperature range of about 10 to about 20°C is preferred when a dehydrating agent is used and the range of about 60 to about 110°C is preferred in other instances.

Reduction of compound (2a) can be achieved by treating (2a) in the presence of about 1 to about 10 equivalents of a catalyst (palladium, $NaBH_4$, $LiAlH_4$, etc.) in alcohol or water at about 25 to about 60°C for about 0.5 to about 10 hours.

The compound (4) can be synthesized by the method of Tamejiro Hiyama et al. [Bull. Chem. Soc. Japan., 45, 1863-1866 (1972)].

Reaction c)



wherein ring A, R^1, R^2, R^3, R^4, L and X have the same meanings defined hereinbefore; R^7 represents an optionally protected amino.

The above reaction c) is directed to cyclization of semicarbazone derivative (5) to synthesize a compound of the present invention. The cyclization reaction is carried out in an inert solvent or in the absence of a solvent, optionally in the presence of a Lewis acid or a Lewis base. The reaction is generally conducted at a temperature within the range from about 0 °C to about 200 °C. In particular, the reaction temperature of about 5 to about 30 °C is preferred when a hydroxyl-activating agent (e.g. trifluoroacetic anhydride, acetic anhydride, phosphorus oxychloride, etc.) is employed. Where no hydroxyl-activating agent is employed, the reaction is carried out at about 100 to about 200 °C, preferably at about 140 to about 180 °C. As the reaction solvent, virtually any inert organic solvent can be employed. Thus, such solvent includes aliphatic and aromatic hydrocarbons (e.g. benzene, ligroin, benzine, toluene, xylene, etc.), halogenated hydrocarbone (e.g. methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphoric triamide, etc.), N-methylpyrrolidone, dimethyl sulfoxide, tetramethylenesulfone, mercaptoacetic acid, pyridine, etc. To remove the residual hydroxyl-activating agent after the reaction, an organic base such as pyridine, triethylamine, dimethylpyridine, etc. or an inorganic base such as potassium hydroxide, sodium hydroxide, etc. can be employed.

This reaction may be conducted in the presence of a dehydrating agent, such as dicyclohexylcarbodiimide, carbonyldiimidazole and so on.

The tetrahydrotriazine compound (1a) thus obtained can be reduced in the manner described for reaction b) to give the hexahydrotriazine compound (1b).

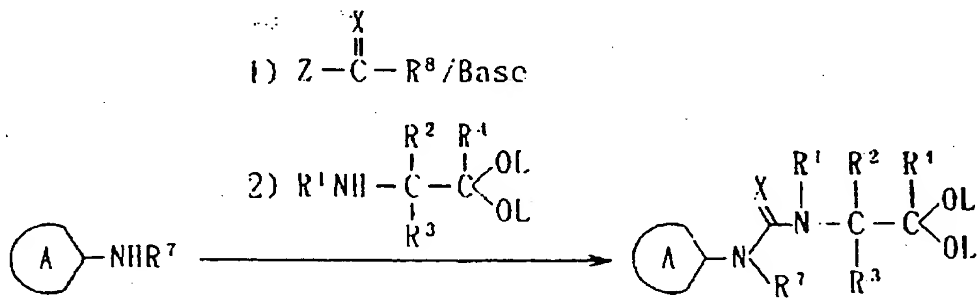
Furthermore, when the 3,3-disubstituted semi-carbazide derivative (6) is used as an intermediate, it can be heat-cyclized in the same manner as th compound (5) to synthesize the tetrahydrotriazine compound (1a). The cyclization reaction is carried out gen rally at a temp rature of about 60 to about 160 °C, pr ferably about 80 to about 120 °C. This reaction can also be conducted with the aid of a catalyst, that is to say in th presence of a Lewis acid or th like (e.g. trifluoroboran etherate, m than sulfonic acid, sulfuric acid, hydrochloric acid, phosphoric acid, polyphosphoric acid, etc.). In this r action, the protection group for the optionally protect d amino represent d by R^7 is any group generally used in organic chemistry [c.f. Shinjikken Kagaku koza Vol. 14, p.2555 Edit. Nihon seikagakkai].

The compound (6), wherein R^7 is amino, can be obtained by a process which comprises dissolving an N-alkyl-N-(2,2-dialkoxyethyl)-N'-phenylurea in an aprotic solvent (e.g. dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone, etc.), adding a finely divided (ca. 50 - 100 µm) powder of potassium hydroxide or sodium hydroxide, then adding an aminating agent (e.g. hydroxyamino-O-sulfonic acid, 3-chloro-2-cyanopherethoxy amine, etc.) in a few portions under vigorous stirring at about 0 to about 10°C, further stirring the reaction mixture at about 25 to about 30°C for another 2 hours, pouring it in iced water, neutralizing the mixture with diluted hydrochloric acid, and extracting it with chloroform.

The N-alkyl-N-(2,2-dialkoxyethyl)-N'-phenylurea can be synthesized by the conventional reaction between phenyl isocyanate and N-2,2-dialkoxyethylamine.

The compound (6) in which R^7 is a protected amino can be obtained by following reaction (c).

Reaction d)



(6)

wherein A, R^1, R^2, R^3, R^4, R^7, L and X have the same meanings defined hereinbefore; R^8 is halogen atom or an optionally substituted C_{1-4} alkoxy (e.g. halo C_{1-4} alkyl etc.) or phenoxy and Z is halogen atom.

The above reaction (d) is directed to an amination followed by an acylation of a hydrazine derivative in the presence of base to provide compound (6). The reaction is generally conducted at a temperature with in the range of about -5 to about 40°C, preferably about 5 to about 10°C. The base used therein includes an organic base such as pyridine, triethylamine, DBU, collidine, 1,1,3,3-tetramethylguanizine and so on.

As the reaction solvent, virtually any inert organic solvent can be employed. Thus, such solvent includes aliphatic and aromatic hydrocarbons (e.g. benzene, ligroin, benzine, toluene, xylene, etc.), halogenated hydrocarbone (e.g. methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphoric triamide, etc.), N-methylpyrrolidone, dimethyl sulfoxide, tetramethylenesulfone, mercaptoacetic acid, pyridine, etc.

Of the compounds of this invention, species in which position-5 represents =S can be obtained by a process which comprises heating a 1,2,4-triazine-1,3-dione compound (which can be synthesized in accordance with the manner reported by Max W. Miller et al., J. Med. Chem., 22, 1483, 1979) with Lawesson's reagent or phosphorus pentasulfide in a solvent such as aliphatic or aromatic hydrocarbons which may optionally be substituted (e.g. benzene, ligroin, benzine, toluene, xylene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), and ketones (e.g. methyl ethyl ketone etc.). The thus-synthesized 5-thion (=S) compound can be reduced with the aid of Raney nickel to give the 5-methylene compound.

The compound (1) and physiologically acceptable salt of the present invention are suitable for the control of parasitic protozoa encountered in the husbandry and/or production of animals such as mammals, birds, fish or insects and show activity against individual or all stages of growth of such pathogenic parasitic protozoa. Furthermore, these compounds show sufficiently effective activity within th usual range of doses against the protozoa which are resistant to the known drugs. As a result, morbidity and th mortality of host animals are decreased and, hence, the efficiency of animal production and reproduction (e.g. the efficiency of production of meat, milk, furs, hides and skins, eggs, honey, etc. as well as the efficiency of breeding)

are increased. Moreover, use of the compound of the present invention enables conomical raising of various animals with good efficiency by preventing protozoal infection such as coccidial infection.

The protozoan diseases that can be controlled by the compound of this invention are of a broad range. Thus, the parasitic protozoa that can be controll d include, among others, protozoa of th Apicomplexa, particularly of the family Eimeriidae, such as the genus Eimeria, e.g. E. acervulina, E. adenoides, E. alabamensis, E. arloinqi, E. auburnensis, E. bovis, E. brunetti, E. canis, E. contorta, E. ellipsoidalis, E. falciformis, E. gallopavonis, E. hagani, E. intestinalis, E. magna, E. maxima, E. meleagridis, E. meleagrimitis, E. mitis, E. mivati, E. necatrix, E. ninakohlyakimovae. E. ovis, E. parva, E. pavonis, E. perforans, E. piriformis, E. praecox, E. stiedai, E. suis, E. tenella, E. truncata, E. zuernii, etc., the genus Isospora such as I. belli, I. canis, I. felis, I. rivolta, I. suis, etc., Toxoplasma gondii, and the genus Cryptosporidium, particularly Cryptosporidium s.p., the family Sarcocystidae, e.g. S. bovicanis, S. bovihominis, S. ovicanis, S. ovifelis, S. suihominis, etc., the genus Leucocytozoon, e.g. L. simondi , L. caulleryi, etc., the family Plasmodiidae, e.g. P. berghei, P. falciparum, P. malariae, P. ovale, P. vivax, etc., protozoa of the subclass Piroplasmea, more specifically of the genus Babesia, e.g. B. argentina, B. bovis, B. canis, etc., the genus Theileria, e.g. T. parva etc., Adeleina, Hepatozoon canis and so on.

Furthermore, protozoa taxonomically belonging to Myxospora or Microspora, protozoa of the genus Glugea and those of the genus Nosema may also be mentioned.

The compound (1) and its physiologically acceptable salt can be used both prophylactically and therapeutically in protozoan infections in mammalian animals (e.g. cattle, horse, swine, sheep, goat, camel, buffalo, donkey, rabbit, deer, reindeer, mink, chinchilla, raccoon, mouse, rat, guinea pig, golden hamster, dog, cat, etc.), birds (e.g. chicken, quail, goose, turkey, duck, wild duck, dove, pigeon, etc.), fresh-water and sea-water fishes (e.g. carp, eel, trout, smelt fish, salmon, ruffer, sole) flatfish, seabream, sea bass, catfish, etc.) and even in insects such as honey bees.

The compound (1) and its physiologically acceptable salt can be safely administered to any of the above-mentioned animals, either as they are or in various dosage forms according to the route of administration which may be oral or parenteral. The dosage forms mentioned above can be manufactured by the per se known methods (e.g. Japanese patent application unexamined publication No. H5-1047 which corresponds to EP-A-476439, Japanese patent application unexamined publication No. H5-117250 which corresponds to EP-A-457015, Japanese patent application unexamined publication No. H2-240003 which corresponds to EP-A-383285, Japanese patent application unexamined publication No. S62-61972 which corresponds to EP-A-215354, etc.).

The compound of the general formula (1) or physiologically acceptable salt thereof in the present invention can be used for preparing a prophylactic and therapeutic agent for protozoal disease by mixing them with a pharmaceutically acceptable additive(s) such as a diluent and an excipient, if necessary, to formulate the antiprotozoal composition according to a known pharmaceutical method, and then incorporated in feed or drinking water for administration.

The antiprotozoal agent of the present invention is prepared, for example, by diluting a compound of the general formula (1) or its physiologically acceptable salt, independently or in a mixed state, with a solid or liquid carrier, by undiluting them, or by stabilizing them by coating and the like to formulate powders, dusts, granules, tablets, solutions, emulsions, pastes, capsules, premixed, injections and the like. The antiprotozoal agent of the present invention is also prepared by dispersing directly the compound of the general formula (1) or its physiologically acceptable salt in feed, drink and the like, or by incorporating therein after dispersed in a carrier. The carrier may be any one, as long as it is physiologically harmless per se. The carriers which function as feed or a component of feed are preferable. The solid carriers include, for example, lactose, sucrose, starch, wheat meal, corn meal, wheat bran, soybean cake, extracted rice bran, rape seed cake, soybean crude meal, cellulose yeast, fish meal, peanut meal, shell powder and calcium carbonate. Examples of the liquid carriers include water, physiological saline and physiologically acceptable organic solvents. In addition, other suitable adjuvants such as emulsifiers, dispersants, suspension aids, wetting agents, thickening agents, gel forming agents and solubilizers may be added in suitable amounts. There may be further incorporated preservatives, fungicides, colorants, aromatics, antibacterial agents, antibiotics, enzyme preparations, lactobacillus preparations, antifebriles, analgesics, antiphlogistics and so on, and other agents for protozoal dis ase may also be compound d in combination as long as they ar differ nt from the compound of the pr s nt inv ntion in mechanism of action. Furthermore, various vitamins, minerals and amino acids may be incorporated.

The antiprotozoal agents of the pr s nt inv ntion are administered to animals such as mammals, birds, fish or insects, for th purpose of prophylaxis or/and treating protozoal diseas . Since in the live-stock industry, domestic animals are usually bred or farmed in groups, it is also included in the scope of this invention of course to administer the antiprotozoal agents of the present invention to inf cted individuals

isolated from the group or to the whole of the group through feed, drinking water and the like, when it has been confirmed that some animals in the group are attacked with protozoal disease.

The antiprotozoan composition of this invention may contain one or more species of the compound or salt of this invention. Furthermore, the composition may contain other drugs for improving the general condition of animals or drugs for prophylaxis or therapy of the indicated disease. It can be used in combination with such drugs unless adverse interactions or dilution of efficacy is foreseen.

The antiprotozoal composition of this invention should contain compound (I) or a physiologically acceptable salt thereof in a concentration of about 0.01 ppm to about 1%, preferably about 0.1 ppm to about 0.1%. In the case of a preparation for extemporaneous dilution, it is prepared so as to contain the active drug in a concentration of about 0.01 to about 90% or, preferably, about 0.1 to about 30%.

Generally, the antiprotozoal composition of this invention can be administered in a daily dose of about 0.01 to about 50 mg/kg body weight, preferably about 0.1 to about 5 mg/kg body weight, as compound (I) or a salt. By way of illustration, the antiprotozoan composition of this invention can be admixed into the animal ration or diet at the level of, as compound (I) or a salt thereof, about 0.01 to about 100 ppm, preferably about 0.1 to about 50 ppm. The resulting ration can be used for both therapeutic and prophylactic purposes. Such a ration can be generally prepared by manufacturing a concentrate or premix containing about 0.5 to about 30 weight %, preferably about 1 to about 20 weight %, of compound (I) or salt with a feed excipient and blending it with a regular feed. The excipient mentioned just above may for example be a corn meal or corn-soya meal containing a small quantity of some dust-preventive edible oil such as corn oil or soybean oil or a mineral salt. The resulting premix is evenly admixed into a regular animal diet for administration.

For the treatment or prevention of coccidiosis in poultry, particularly in chickens, quails, ducks, wild ducks, geese, and turkeys, generally about 0.01 to about 100 ppm, preferably about 0.1 to about 50 ppm, of compound (I) or salt is administered as previously mixed with suitable edible materials such as nutrient feeds. The drug can be added to drinking water for ingestion.

For the treatment of animals, e.g. for the therapy of coccidiosis or toxoplasmosis, compound (I) or a physiologically acceptable salt thereof is administered in a daily dose of about 0.5 to about 100 mg/kg body weight. Depending on the body weight of animals, therapeutic regimen, species or breeds of animals, individual responses to the antiprotozoan drug, dosage form or formulation, timing and intervals of administration, etc., it may at times be necessary to depart from the above-mentioned dosage range. Thus, a reduced dose may prove effective in some cases, while an increased dose may be necessary in other cases. For massive administration, the daily dosage may be advantageously administered in divided doses.

The treatment of fish is carried out by the oral route, such as through feed, or by the short-time "drug bath" method which comprises transferring the fish from the farming-pond to a tank filled with drug solution (drug bath) and keeping them therein for a predetermined time (ranging from a few minutes to several hours).

However, a temporary or permanent treatment of the whole habitat (for example a pool, aquarium, tank or pond) can also be instituted.

In such cases, compound (I) or a physiologically acceptable salt is applied in a form suited to the particular situation. The concentration of the antiprotozoal agent of this invention may range from about 1 ppm to about 10 weight per volume %.

For the "drug bath" treatment or the omnibus habitat treatment (pool treatment) of fish, it is preferable to employ a solution of the antiprotozoan drug of this invention in a polar solvent or solvent mixture which can be diluted or suspended with water.

To prepare such a solution, compound (1) or a physiologically acceptable salt is dissolved or suspended in a polar water-soluble vehicle. It is preferable that after addition of the compound (1) or/and physiologically acceptable salt the vehicle shows a pH range of 7 to 10, especially about 8 to 10.

Since administration of the compound of this invention controls parasitic protozoan to thereby decrease the incidence of the associated diseases and death and improve the growth retardation and deteliorated gen ral condition, the invention is useful for preventing the decrease of yields in the production of meat, milk, furs, eggs, honey and so on. Moreover, the invention also contributes remarkably to a safe husbandry of ornamental animals and pets.

The following examples, test examples and formulation examples ar intended to describe this invention in further detail and should by no means be construed as d fining the scop of the invention. The chemical structure of the compound obtain d in the following Exampl s are shown in the Table 3.

Test Example 1 Effect on Biological Test (1)

The anticoccidal effect of the compound of this invention was evaluated in chickens. Using 9-day-old male white Leghorn chicks in groups of 3, the animals in all groups except the non-infected, untreated control group were orally inoculated with 5×10^4 sporulated oocysts/bird of the laboratory standard strain of Eimeria tenella. As the drug, a dried, crushed batch of the compound of this invention was admixed with 31.3 ppm of the standard basal ration (SDL No. 1; Nippon Haigo Shiryo Co., Ltd.) and the chicks were allowed free access to the resulting diet for 9 consecutive days beginning 24 hours before the infection until day 8 after the infection. During the feeding period, the body weight gain of each chick was determined. Furthermore, the number of bloody droppings was counted and the count of excreted oocysts was taken to evaluate the anticoccidial effect of the drug. The results are shown in Table 1. In the table, Compound No. corresponds to the Compound No. in Table 3.

Table 1

Compound No.	Relative body weight gain (%)[1]	Number of bloody droppings[2]	OPG[3] (log)
Non-infected/ treatment group	100	0	ND[4]
Infected/untreated control group	40.2	3.0	5.2
1	100	0	ND
2	102.9	1.25	ND
3	96.1	0	ND
4	91	0	ND
5	100	0	ND
6	100	0	ND
7	104.4	0	ND
15	100	0	ND
22	111.9	0	ND
38	100	0	ND
39	100	0	ND
40	100	0	ND
43	100	0	ND
44	100	0	ND
45	104.6	0	ND

1)

$$\text{Relative body weight gain} = \frac{\text{Average body weight gain in treatment group}}{\text{Average body weight gain in non-infected control group}} \times 100$$

2) Number of bloody droppings: The number of blood droppings per bird as detected on the paper set under the floor-net on the peak day of excretion from the intestine of the chick.

3) OPG: The number of oocysts excreted in 1 gram of feces (on day 7 after infection)

4) ND: Not detected.

It is apparent from the data in Table 1 that compared with the infected group, the groups treated with the compound of this invention invariably showed a relative body weight gain, indicating that the compound of this invention has excellent anticoccidial activity.

Test Example 2 Effect on the Biological Test (2)

The anticoccidial effect of the compound of the invention was evaluated following the method in the Test Example 1 by administration of the standard ration containing 4 ppm of the compound. The results are shown in Table 2.

Table 2

Compound No.	Relative body weight gain (%)	Number of bloody droppings)	OPG (log)
Non-infected/treatment group	100	0	ND
Infected/untreated control group	40.2	3.0	5.2
53	92.3	0	ND
54	90.7	0	ND
55	92.2	0	ND
56	95.7	0	ND
57	95.8	0	ND
58	95.7	0	ND
59	92.2	0	ND
60	90.3	0	ND
61	90.3	0.7	ND
62	94.5	0	ND
65	90.0	0	ND
66	98.4	0	ND
67	92.6	0	ND
68	97.0	0	ND
69	94.1	0.2	ND

Reference Example 1

3,5-dichloro-4-(4'-chloro-1-methoxycarbonyl)benzyl nitrobenzene

In 100 ml acetonitrile was dissolved 4.00 g p-chlorophenyl acetate, 4.54 g 3,4,5-trichloronitrobenzen and 2.60 g 1,1,3,3-tetramethyl guanidine followed by refluxtion for 8 hours and concentrated to dryness. The residue was dissolved with 100 ml toluene, washed with 100 ml iced water and 100 ml cold water, dried over $MgSO_4$ and concentrated. After the concentrate was added ethanol, 6.82 g of the title compound was filtlated as crystals. m.p. 92-93 • C

Reference Example 2

3,5-dichloro-4-(4'-chloro-methoxycarbonyl)benzylaniline

In 50 ml of ethanol was dissolved 6.00 g 3,5-dichloro-4-(4'-chloro-methoxycarbonyl)benzylnitrobenzen prepared according to Reference Example 1 followed by addition of 5-fold molar $SnCl_2$ and refluxed for 2 hours after the reaction solution was concentrated, powdered in 1 l iced water and extracted with 100 ml of ethyl acetate, after the solution was made to be alkaline by adding 10% NaOH. The extract was washed with water, dried over $MgSO_4$ and recrystalized with ethanol to provide 5.12 g of th title compound. m.p. 151-152 • C

Reference Example 3

3,5-dichloro-4-(4'-chloro-1-methoxycarbonyl)benzylphenylhydrazine

In the mixture of 100 ml of acetic acid and 30 ml of hydrochloride was dissolved 5.00 g of 3,5-dichloro-4-(4'-chloro-1-methoxycarbonyl)benzylaniline prepared according to Reference Example 2 followed by addition of 10 ml of 2-fold molar sodium nitrate solution dropwise with stirring at 5 - 10 °C.

After completion of the addition, the solution was reacted at 10 - 20 °C for 2 hours and further reacted at 10-20 °C for 2 hours after addition of 5-fold molar $SnCl_2$ dissolved in 50 ml hydrochloride dropwise with stirring at 5 - 10 °C. The crystals thus obtained was suspended in iced water and extracted with ethyl acetate. The extract was dried over $MgSO_4$, concentrated and recrystalized to give 4.20 g of the title compound. m.p. 113-114 °C

Reference Example 4

4-(4'-chloro-1-methoxycarbonyl)benzyl-3-trifluoromethyl aniline

Starting with 4-(4'-chloro-1-methoxycarbonyl)benzyl-3-trifluoromethylnitrobenzene, the title compound was synthesized in otherwise a similar manner as Reference Example 2. m.p. 103-104 °C

Reference Example 5

4-(4'-chloro-1-methoxycarbonyl)benzyl-3-trifluoromethylphenyl hydrazine

Starting with 4-(4'-chloro-1-methoxycarbonyl)benzyl-3-trifluoromethylaniline prepared according to Reference Example 4, in otherwise a similar manner as Reference Example 3. m.p. 95-97 °C

Example 1

2-(3,5-Dichlorophenyl)-5-methoxy-2,3-dihydro-1,2,4-triazin-3-one (Compound No. 16)

In THF was dissolved 2.77 g of 2-(3,5-dichlorophenyl)-5-chloro-2,3-dihydro-1,2,4-triazin-3-one followed by addition of sodium methoxide in an equimolar amount to the starting compound, and the mixture was stirred at room temperature for 1 hour. After completion of this reaction, the reaction mixture was concentrated under reduced pressure and ice-water was added to the residue. The resulting crystals were collected by filtration, dried and dissolved in 100 ml of chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, concentrated and purified by column chromatography (Merck Silica Gel 60; dichloromethane-methanol = 10:1) to provide 0.4 g of white crystals (m.p. 164 °C).

Elemental analysis for $C_{10}H_7Cl_2N_3O_2$			
	C	H	N
Calcd.:	44.14;	2.59;	15.44
Found :	43.92;	2.61;	15.31

NMR [$CDCl_3$] δ: 4.09 (s, 3H), 7.25-7.48 (m, 1H), 7.51-7.75 (m, 2H)

Example 2

2-[3,5-Dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]hexahydro-1,2,4-triazin-3-one (Compound No. 38)

To 50 ml of dichloromethane was added 2.07 g of 2-[3,5-dichloro-4-(4'-chloro-1-cyanob nzyl)phenyl]-1-(2-hydroxyethyl)semicarbazide as w ll as 2-fold molar of pyridine. The solution was cool d to 0 to 5 °C and equimolar of trifluoroacetic anhydride was added dropwise with constant stirring. Aft r completion of the dropwise addition, the reaction was further carried out und r th same conditions for one hour. The dichloromethan was th n removed by concentration and 50 ml of 1,4-dioxane was added to the concentrate. The mixture was r fluxed for 4 hours, after which the solvent was distilled off and the residue

was dissolved in chloroform. The chloroform solution was washed with iced water, dried over anhydrous magnesium sulfate and concentrated. This residue was further purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 0.1 g of the title compound as a white substance melting at 138 - 139 °C (dec.).

Elemental analysis for $C_{17}H_{13}Cl_3N_4O$			
	C	H	N
Calcd.:	51.60;	3.31;	14.16
Found :	51.53;	3.36;	14.14

NMR [$CDCl_3$] δ: 3.00-3.64 (m, 4H), 4.19 (t, J=6Hz, 1H), 5.69 (br, 1H), 6.09 (s, 1H), 7.29 (s, 4H), 7.92 (s, 2H)

Example 3

2-[3,5-Dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (Compound No. 41)

Starting with 2.00 g of 2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]-1-(2-hydroxymethyl-methylidene semicarbazone, 0.38 g of the white title compound was synthesized in otherwise the same manner as Example 2. m.p. 166-167 °C

Elemental analysis for $C_{17}H_{11}Cl_3N_4O$			
	C	H	N
Calcd.:	51.86;	2.82;	14.23
Found :	51.60;	2.87;	13.93

NMR [$CDCl_3$] δ: 4.00-4.20 (m, 2H), 6.14 (s, 1H), 6.45 (br, 1H), 7.15 (br, 1H), 7.30 (s, 4H), 7.72 (s, 2H)

Example 4

2-[3,5-Dichloro-4-(4-chloro-1'-cyanobenzyl)phenyl]-4-methylhexahydro-1,2,4-triazin-3-one (Compound No. 40)

In 50 ml of dimethylformamide was dissolved 1.18 g of 1-methyl-1-(2,2-diethoxyethyl)-2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]semicarbazide and the reaction was carried out at 140 - 145 °C with stirring for 2 hours. The reaction mixture was then poured in 300 ml of iced water and extracted with 200 ml of chloroform. The extract was dried over anhydrous magnesium sulfate, concentrated to dryness. The residue was reducted with $LiA1H_4$ in THF and purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 0.1 g of the title compound. m.p. 137 - 138 °C.

Elemental analysis for $C_{18}H_{15}Cl_3N_4O$			
	C	H	N
Calcd.:	52.77;	3.69;	13.68
Found :	52.74;	3.62;	13.68

NMR [$CDCl_3$] δ: 3.00 (s, 3H), 3.20-3.60 (m, 4H), 4.25 (br, 1H), 6.08 (s, 1H), 7.28 (s, 4H), 7.89 (s, 2H)

Example 5

2-(3,5-Dichlorophenyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-one-5-thione (Compound No. 7)

To 100 ml of toluene was added 2.58 g of the starting compound 3,5-dione as well as 1/2 equivalent of Lawesson's reagent and the mixture was refluxed for 5 hours. The reaction mixture was then concentrated and purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 0.9 g of light-yellow crystals, m.p. 200 - 201 °C.

Elemental analysis for $C_9H_5Cl_2N_3OS$			
	C	H	N
Calcd.: Found :	39.43; 39.45;	1.84; 1.97;	15.33 15.05

NMR [$CDCl_3$] δ: 7.67 (s, 3H), 7.84 (s, 1H), 13.80 (br, 1H)

Example 6

2-(3,5-Dichlorophenyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (Compound No. 1)

In 50 ml of 70% ethanol was dissolved 2.74 g of Compound No. 7, synthesized in Example 5, followed by addition of 10 equivalents of activated Raney nickel. The mixture was stirred at room temperature overnight, after which the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure and the residue was dissolved in 100 ml of ethyl acetate. This solution was dehydrated over anhydrous magnesium sulfate, concentrated and the resulting red-brown oil was purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 1.0 g of the title compound as a pale yellow substance. m.p. 179 - 181 °C

Elemental analysis for $C_9H_7Cl_2N_3O$			
	C	H	N
Calcd.: Found :	44.29; 44.59;	2.89; 2.98;	17.22 17.41

NMR [$CDCl_3$] δ: 4.05-4.20 (m, 2H), 6.30-6.60 (br, 1H), 7.00-7.30 (m, 2H), 7.52 (d, J=2Hz, 2H)

Example 7

2-(3,5-Dichlorophenyl)-5-phenyl-2,3-dihydro-1,2,4-triazin-3-one (Compound No. 27)

In 50 ml of dioxane was dissolved 2.20 g of 2-(3,5-dichlorophenyl)semicarbazidefollowed by addition of 1.52 g of phenylglyoxal monohydrate, and the mixture was refluxed for 5 hours. The reaction mixture was then concentrated and the residue was recrystallized from acetonitrile to provide 1.34 g of the title compound. m.p. 160 - 161 °C..

Elemental analysis for $C_{15}H_9Cl_2N_3O$			
	C	H	N
Calcd.: Found :	56.63; 56.52;	2.85; 2.78;	13.21 13.34

NMR [$CDCl_3$] δ: 7.38 (t, J=2Hz, 1H), 7.45-7.70 (m, 3H), 7.75 (d, J=2Hz, 2H), 8.05-8.30 (m, 2H), 8.48 (s, 1H)

Example 8

Starting with 2-(3,5-dichlorophenyl)-1-(2-hydroxy-2-methylpropylidene)semicarbazone, Compound 2 was synthesized in otherwise a similar manner as Example 2. m.p. 120-122 °C

Example 9

Starting with 2-(3,5-dichlorophenyl)-1-(2-hydroxy-2-methylthioethylidene)semicarbazone, Compound 3 was synthesized in otherwise a similar manner as Example 2. m.p. 115-116 °C

Example 10

Starting with 2-(3,5-dichlorophenyl)-1-(2,2-dimethylthio-2-hydroxyethyl)semicarbazide, Compound 4 was synthesized in otherwise a similar manner as Example 2. m.p. 151-152 °C

Example 11

Starting with Compound 1, Compound 5 was synthesized in otherwise a similar manner as Example 4. m.p. 148-149 °C

Example 12

Starting with 2-(3,5-dichlorophenyl)-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one-5-thione, Compound 6 was synthesized in otherwise a similar manner as Example 6. m.p. 164-165 °C

Example 13

Starting with 2-(3,5-dichlorophenyl)-4-methyl-hexahydro-1,2,4-triazin-3,5-dione, Compound 8 was synthesized in otherwise a similar manner as Example 5. m.p. 149-150 °C

Example 14

Starting with 2-(2,5-dichlorophenyl)-hexahydro-1,2,4-triazin-3,5-dione,Compound 9 was synthesized in otherwise a similar manner as Example 5. m.p. 221-223 °C (dec)

Example 15

Starting with 2-(3,5-dichlorophenyl)-1-(2-hydroxy-2-phenylethyl)semicarbazide, Compound 10 was synthesized in otherwise a similar manner as Example 2. m.p. 164-165 °C

Example 16

Starting with 2-(3,5-dichlorophenyl)-1-(2-hydroxy-2-phenylethylidene)semicarbazone, Compound 11 was synthesized in otherwise a similar manner as Example 2. m.p. 139-140 °C

Example 17

Starting with Compound 8, Compound 12 was synthesized in otherwise a similar manner as Example 6. m.p. 210-211 °C

Example 18

Starting with 2-(3,5-dichlorophenyl)-6-methylhexahydro-1,2,4-triazin-3-one-5-thion , Compound 13 is synthesized in otherwise a similar manner as Example 6.

Example 19

Using methyl mercaptan in place of sodium methoxide, Compound 14 was synthesized in otherwise a similar manner as Example 1. m.p. 190-191 • C

Example 20

Using benzyl mercaptan in place of sodium methoxide, Compound 15 was synthesized in otherwise a similar manner as Example 1. m.p. 152-153 • C

Example 21

5-chloro-2-(3,5-dichlorophenyl)-2,3-dihydro-1,2,4-triazine-3-one (compound No. 17)

In 30 ml of dichloromethane suspended with 1.00 g of 2-(3,5-dichlorophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dionefollowed by addition of 2-fold morlar each of carbone tetrachloride and triphenylphosphine and refluxed for 12 hours. After the completion of the reaction, the resulted solution were purified by colomun chlomatography (Merck Silica Gel 60 dichloromethane-carbontetrachloride = 2:1). m.p. 148-149 • C

NMR [$CDCl_3$] δ: 7.42(t,J = 2Hz,1H), 7.66(d,J = 2Hz,2H), 7.91(s,1H)

Example 22

Using potassium fluoride in place of sodium methoxide, Compound 18 was synthesized in otherwise a similar manner as Example 1. m.p. 93-95 • C

Example 23

Using p-chlorothiophenol in place of sodium methoxide, Compound 19 was synthesized in otherwise a similar manner as Example 1. m.p. 176-178 • C

Example 24

Using t-butyl mercaptan in place of sodium methoxide, Compound 20 was synthesized in otherwise a similar manner as Example 1. m.p. 97-99 • C

Example 25

Using potassium t-butoxide in place of sodium methoxide, Compound 21 was synthesized in otherwise a similar manner as Example 1. m.p. 91-92 • C

Example 26

Using phenol in place of sodium methoxide, Compound 22 was synthesized in otherwise a similar manner as Example 1. m.p. 126-127 • C

Example 27

Using cyclopropylmethanol in place of sodium methoxide, Compound 23 was synthesized in otherwise a similar manner as Example 1. m.p. 68-69 • C

Example 28

Using 2-fluoroethanol in place of sodium methoxide, Compound 24 was synthesiz d in otherwise a similar manner as Example 1. m.p. 110-111 • C

Example 29

Using 2,2,2-trifluoroethanol in place of sodium methoxide, Compound 25 was synthesized in otherwise a similar manner as Example 1. m.p. 80-81 °C

Example 30

Using 1,3-dimercaptopropane in place of sodium methoxide, Compound 26 was synthesized in otherwise a similar manner as Example 1. m.p. 195-196 °C

Example 31

Starting with 2-(3,5-dichlorophenyl)-5-chloro-2,3,4,5-tetrahydro-1,2,4-triazin-3-one and using methyl mercaptan in place of sodium methoxide, Compound 3 was synthesized in otherwise a similar manner as Example 1. m.p. 115-116 °C.

Example 32

Using 2-(3,5-dichlorophenyl)-1-benzoylmethylidenesemicarbazone, Compound 27 was synthesized in otherwise a similar manner as Example 2. m.p. 160-161 °C

Example 33

Using 2-(3,5-dichlorophenyl)-1-benzoyl-1-phenylmethylidenesemicarbazone, Compound 28 was synthesized in otherwise a similar manner as Example 2. m.p. 158-159 °C

Example 34

Starting with 2-(3,5-dichlorophenyl)-5-chloro-1,2,3,6-tetrahydro-1,2,4-triazin-3-one and using methyl mercaptan in place of sodium methoxide, Compound 29 was synthesized in otherwise a similar manner as Example 1. m.p. 133-134 °C

Example 35

Using 2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazin-3,5-dione, Compound 30 was synthesized in otherwise a similar manner as Example 5. m.p. 183-184 °C

Example 36

Starting with 2-phenyl-5-chloro-2,3-dihydro-1,2,4-triazin-3-one and using methyl mercaptan in place of sodium methoxide, Compound 31 was synthesized in otherwise a similar manner as Example 1. m.p. 115-116 °C

Example 37

Starting with 2-phenyl-5-chloro-2,3-dihydro-1,2,4-triazin-3-one, Compound 32 was synthesized in otherwise a similar manner as Example 1. m.p. 102-103 °C

Example 38

Using 2-(4-chlorophenyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3,5-dione, Compound 33 was synthesized in otherwise a similar mann r as Example 5. m.p. 198-199 °C

Example 39

Starting with 2-(4-chlorophenyl)-5-chloro-2,3-dihydro-1,2,4-triazin-3-on and using methyl mercaptan in place of sodium methoxide, Compound 34 was synthesiz d in otherwise a similar manner as Exampl 1. m.p. 168-169 °C

Example 40

Using 2-(4-chlorophenyl)-5-chloro-2,3-dihydro-1,2,4-triazin-3-one, Compound 35 was synthesized in otherwise a similar manner as Example 1. m.p. 151-152 °C

Example 41

Using 2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3,5-dione, Compound 36 was synthesized in otherwise a similar manner as Example 5. m.p. 249-250 °C

Example 42

Using 2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]hexahydro-1,2,4-triazin-3,5-dione, Compound 37 was synthesized in otherwise a similar manner as Example 5. m.p. 215-216 °C (dec)

Example 43

Using 2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]-4-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one-5-thione, Compound 40 was synthesized in otherwise a similar manner as Example 6. m.p. 137-138 °C

Example 44

Using 2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]-5-chloro-2,3-dihydro-1,2,4-triazin-3-one, Compound 42 was synthesized in otherwise a similar manner as Example 1. m.p. 193-194 °C

Example 45

Compound 36 was dissolved in THF and reacted with equimolar of methyl iodide to provide Compound 43. m.p. 204-205 °C

Example 46

Compound 43 was dissolved in dichloromethane and reacted with chlorine gas to provide Compound 44. m.p. 184-185 °C

Example 47

2-(3,5-dichlorophenyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 1)

In 20 ml acetonitrile was dissolved 1.77 g of 3,5-dichlorophenylhydrazine followed by addition of 1.10 g benzaldehyde dropwise with constant stirring at 10 to 20 °C and obtained 2.70 g hydrazone. In 30 ml of acetonitrile was dissolved 1.33 g of the hydrazone followed by the addition of 3-fold mole pyridine, and 0.6-fold mole trichlolomethylchloroformate was added dropwise to the mixture with constant stirring at 0 to 10 °C. After completion of the dropwise addition, the mixture was stirred at 20 to 25 °C for 1 hour.

In 30 ml acetonitrile was dissolved 0.60 g of aminoacetoaldehyde dimethyl acetate followed by the addition of the above prepared reaction solution with constant stirring at 5 to 10 °C. After completion of the dropwise addition, the reaction solution was stirred at 20 to 25 °C for 3 hours. After concentrated the thus obtained reaction solution, iced water was added and extracted with 50 ml of dichloromethane. After dried over anhydrous magnesium sulfate, the extract was concentrated and purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 1.54 g of 1-benzilidene-2-(3,5-dichlorphenyl)-4-(2,2-dimethoxyethyl)semicarbazone as white crystals (m.p. 119-120 °C).

In 20 ml acetonitrile was dissolved 1.00 g of the thus obtained semicarbazon , followed by heat-reaction at 50 to 60 °C with 0.1 ml conc. hydrochloride for 20 minutes. Aft r completed the r action, the resulted crystal was collected by filtration and washed with water. Thus obtained crystal was recrystallized from ethyl acetat to provide 0.72 g the title compound. m.p. 179-181 °C

N

Exampl 48

2-[3,5-dichloro-4-(4-chlorophenylthio)phenyl]-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 45)

After refluxed 1.60 g of 3,5-dichloro-4-(4-chlorophenylthio)phenylhydrazoneand 0.9 g of N-acetonyl-phenylcarbamate in 30 ml toluene, 0.8 g of 1,8-diazabicyclo[5,4,0]-7-undensen was added therein and refluxed 2 more hours. After completed the reaction, the solution was concentrated, added ice water and extracted from 50 ml of dichloromethane. After dried over with anhydrous magnesium sulfate, the extract was concentrated to dryness and purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 0.34 g of the title compound as a white substance. m.p. 258-259 • C

NMR (d_6-DMSO)δ: 2.04(s,3H), 3.98(br-d,J = 2Hz,2H), 7.22(g,J = 8Hz,4H), 7.80(br,1H), 7.88(s,2H)

Example 49

2-[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 46)

Starting with 3,5-dichloro-4-(4-chlorobenzoyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 48. m.p. 257-259 • C

Example 50

4-acetyl-2-[3,5-dichloro-4-(4-chlorobenzyl)phenyl]-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 47)

The title compound was obtained by acetylating the compound 46 prepared according to Example 49 with acetic acid anhydride in toluene. m.p. 101-102 • C

Example 51

2-(3,5-dichlorophenyl)-1-methyl-hexahydro-1,2,4-triazin-3-one(conpound No. 49)

Chrystals obtained by reacting 1-aminoacethyl-1-methyl-2-(3.5-dichrolophenyl) hydrazine with phenyl chloroformate under the existance of a base was dissolved in THF followed by reduction with $NaBH_4$ to provide the title compound m.p. 150-151 • C.

Example 52

6-chloro-2-(3,5-dichlorophenyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-thione (compound No. 49)

In 30 ml dichloromethane 1.33 g of 1-(3,5-dichlorophenyl)-2-benzyldenhydrazone and 5-fold molar pyridine were dissolved followed by addition of 2-fold molar thiophosgen dropwise with constant stirring at 5 to 10 • C. After completed the dropwise addition, the resulting solution was stirred at 20 to 25 for 1 hour and added the equimolar ethylglcinate hydrochloride salt with stirring at 5 to 10 • C. After two hour reaction, the reaction solution was washed with water and concentrated to dryness. The residue was dissolved in 30 ml of acetonitrile and reacted with 0.1 ml conc. hydrochloride at 50 to 60 • C for 20 minutes to provide 2-(3,5-dichlorophenyl)-hexahydro-1,2,4-triazin-6-one-3-thion. The resulted compound was chlorized by known manner to provided the title compound. m.p. 207-208 • C

Example 53

2-[3,5-dichlorophenyl)-1,5-dimethylhexahydro-1,2,4-triazin-3-one (compound No. 50)

Reacting 1-(2-aminopropyl)-1-methyl-2-(3,5-dichloroph nyl)hydrazine with phenyl chloroformate under pr sence of base to provide th title compound. m.p. 129-130 • C

Example 54

2-(3,5-dichlorophenyl)-1-methyl-hexahydro-1,2,4-triazin-3-thione (compound No. 51)

Starting with 1-(2-aminoethyl)-2-(3,5-dichlorophenyl)methylhydrazide and thiophosgene, the title compound was synthesized in otherwise a similar manner as Example 52. m.p. 240-241 °C

Example 55

2-[3-chloro-4-(4'-chloro-1-cyanobenzyl)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 52)

Starting with 3-chloro-4-(4'-chloro-1-cyanobenzyl)-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 192-193 °C

Example 56

2-[3-Chloro-4-(4'-chloro-1-cyanobenzyl)-5-methylphenyl]-hexahydro-1,2,4-triazin-3-one (compound No. 53)

Reducing the compound 52 prepared according to Example 55 with $LiAlH_4$ in THF to provide the title compound. m.p. 201-202 °C

Example 57

2-[3-chloro-4-(4'-chloro-1-cyanobenzyl)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one-5-thione (compound No. 54)

Starting with 2-[3-chloro-4-(4'-chloro-1-cyanobenzyl)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione, the title compound was synthesized in otherwise a similar manner as Example 5. m.p. 234-236 °C

NMR (d_6-DMSO)δ: 2.41(s,3H), 6.36(s,1H), 7.17-7.70(m,6H), 7.87(s,1H), 13.86(br,1H)

Example 58

2-[3-chloro-4-(4'-chloro-1-cyanobenzyl)-5-methylphenyl]hexahydro-1,2,4-triazine-3-one-5-thione (compound No. 55)

Reducing the compound 54 prepared according to Example 57 with $LiAlH_4$ in THF to provide the title compound. m.p. 217-218 °C

Example 59

2-[3,5-dichloro-4-(4'-chloro-1-benzoyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 56)

Starting with 3,5-dichloro-4-(4'-chlorobenzoyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47.
m.p. 212-213 °C

Example 60

2-[3,5-dichloro-4-(4'-chloro-1-hydroxybenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 57)

Reducing the compound 56 prepared according to Example 59 with $LiAlH_4$ in THF to provide th title compound. m.p. 115-116 °C

Example 61

2-[3-chloro-4-(4-chlorobenzoyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 58)

Starting with 3-chloro-4-(4-chlorobenzoyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 158-159 °C

Example 62

2-[3-chloro-4-(4'-chloro-1-hydroxybenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 59)

The compound 58 prepared according to Example 61 was reduced with $LiAlH_4$ in THF to provide the title compound. m.p. 135-136 °C

Example 63

2-[3,5-dichloro-4-(4-chlorophenylthio)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 60)

Starting with 3,5-dichloro-4-(4-chlorophenylthio)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 224-225 °C

Example 64

2-[4-(4-chlorobenzyl)-3-chlorophenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 61)

Starting with 3-chloro-4-(4-chlorobenzyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 196-197 °C

Example 65

2-[3-chloro-4-(2-chloropyridin-5-yl-cyanomethyl)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 62)

Starting with 3-chloro-4-(2-chloropyridin-5-yl-cyanomethyl)-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 211-212 °C

Example 66

2-[3-chloro-4-(2-chlorothiazol-5-yl-cyanomethyl)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 63)

Starting with 3-chloro-4-(2-chlorothiazol-5-yl-cyanomethyl)-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 238-239 °C

Example 67

2-[3-chloro-4-(1-methylimidazol-2-yl-thio)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 64)

Starting with 3-chloro-4-(1-methylimidazol-2-yl-thio)-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 173-174 °C

Example 68

2-[3,5-dichloro-4-(4'-chloro-1-fuluorobenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-on (compound No. 65)

In 20 ml dichloromethane was suspended 0.38 g of the compound 57 followed by addition of 0.16 g of diethylaminosulfurtrifuluoride (DAST) dissolved in 5 ml dropwise with constant stirring at about -50 °C. After

reacted for 30 minutes under same condition, the reaction solution was further reacted at 20-25 °C for 1 hour and concentrated. The residue was purified by column chromatography (Merck Silica Gel 60; chloroform) to provide 0.22 g of the title compound. m.p. 182-183 °C

NMR ($CDCl_3$)δ: 4.09(t,J = 2Hz,2H), 6.65(br,1H), 7.12(t,J = 2H₂,1H), 7.22(d,J = 46Hz,1H), 7.30(s,4H), 7.67(d,J = 2Hz,2H)

Example 69

2-[3-chloro-4-(4-chloro-1-fuluorobenzyl)pheny]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 66)

Starting with 2-[3-chloro-4-(4'-chloro-1-hydroxybenzyl)pheny]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one, the title compound was synthesized in otherwise a similar manner as Example 68. m.p. 124-125 °C

Example 70

2-[3,5-dichloro-4-(4'-chlorobenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 67)

Starting with 3,5-dichloro-4-(4-chlorobenzyl)phenylhydrazine the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 196-197 °C

Example 71

2-[3,5-dichloro-4-(4-chlorophenylthio)phenyl]hexahydro-1,2,4-triazin-3-one (compound No. 68)

The compound 60 was reduced with $LiA1H_4$ in THF to provide the title compound. m.p. 242-243 °C

Example 72

2-[4-(4-chlorobenzyl)-3-chlorophenyl]hexahydro-1,2,4-triazin-3-one (compound No. 69)

The compound 61 was reduced with $LiA1H_4$ in THF to provide the title compound. m.p. 157-158 °C

Example 73

2-(2-chloro-4-trifluoromethylpyridin-6-yl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 70)

Starting with 2-chloro-4-trifluoromethylpyridin-6-yl-hydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 197-198 °C

Example 74

2-(2-chloro-4-trifluoromethyl-pyridin-6-yl)hexahydro-1,2,4-triazin-3-one (compound No. 71)

The compound 70 prepared according to Example 73 was reduced with $LiA1H_4$ in THF to provide the title compound. m.p. 191-192 °C

Example 75

2-[3,5-dichloro-4-[2-(4-chlorophenyl)-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 72)

Starting with 3,5-dichloro-4-[2-(4-chlorophenyl)-1-cyanoethyl]phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 213-213 °C

Example 76

2-[3,5-dichloro-4-(4'-chloro-1-methoxycarbonylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 73)

Starting with 3,5-dichloro-4-(4'-chloro-1-methoxycarbonylbenzyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 206-207

Example 77

2-[3,5-dichloro-4-(4'-chloro-1-hydroxymethylbenzyl)phenyl]hexahydro-1,2,4-triazin-3-one (compound No. 88)

The compound 73 prepared according to Example 76 was reduced with $LiA1H_4$ in THF to provide the title compound. m.p. 108-109 °C

NMR ($CDCl_3$) δ; 3.00-3.60(br,4H), 4.00-4.70(br-m,4H), 5.12(t,1H), 5.88(br-s,1H), 7.19(s,4H), 7.73(s,2H)

Example 78

2-[3-trifluoromethyl-4-(4'-chloro-1-methoxycarbonylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 74)

Starting with 3-trifluoromethyl-4-(4'-chloro-1-methoxycarbonylbenzyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 118-119 °C

Example 79

2-[3-chloro-4-(4-chlorobenzyl)-5-methylphenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 89)

Starting with 3-chloro-4-(4-chlorobenzyl)-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47.
m.p. 209-210 °C

Example 80

2-[3-chloro-4-(4-chlorobenzyl)-5-methylphenyl] hexahydro-1,2,4-triazin-3-one (compound No. 90)

The compound 89 prepared according to Example 79 was reduced with $LiAlH_4$ in THF to provide the title compound. m.p. 197-198 °C

Example 81

2-[3-chloro-4-(4'-chloro-1-fluorobenzyl)-5-methylphenyl]hexahydro-1,2,4-triazin-3-one (compound No. 91)

Starting with 3-chloro-4-(4'-chloro-1-fluorobenzyl)-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 160-161 °C (dec)

Example 82

2-[3-chloro-4-(4'-chlorophenoxy)-5-methylphenyl]hexahydro-1,2,4-triazin-3-one (compound No. 92)

Starting with 3-chloro-4-(4'-chlorophenoxy)-5-methylphenylhydrazine, the title compound was synthesized in otherwis a similar manner as Example 47 and reduced with $LiAlH_4$ in THF. m.p. 188-189 °C

Example 83

2-[3-chloro-4-(4'-chlorobenzylthio)-5-methylphenyl]hexahydro-1,2,4-triazin-3-one (compound No. 93)

Starting with 3-chloro-4-(4'-chlorobenzylthio)-5-methylphenylhydrazine, the title compound was synth sized in otherwise a similar manner as Example 82. m.p. 165-167 • C

Example 84

2-{3-chloro-4-[2-(4'-chlorophenyl)-2-cyanovinylen]-5-methylphenyl}-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 94)

Starting with 3-chloro-4-[2-(4'-chlorophenyl)-2-cyanovinylene]-5-methylphenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 250-251 • C

Example 85

2-[3-trifluoromethyl-4-(4'-chloro-1-hydroxymethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 95)

The compound 74 prepared in Example 78 was reduced with $LiAlH_4$ in THF to provide the title compound.
m.p. 76-77 • C
Further reduction of the title compound in THF with $LiAlH_4$, and obtained 2-[3-trifluoromethyl-4-(4'-chloro-1-hydroxymethylbenzyl)phenyl]-hexahydro-1,2,4-triazin-3-one (compound No. 77).
m.p. 87-88 • C

Example 86

2-[3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenyl]-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 39)

Starting with 3,5-dichloro-4-(4'-chloro-1-cyanobenzyl)phenylhydrazine is disolved into toluene and heated with acetonylamine for two hours. After adding equimolar of phenyl chloroformate, the result solution was heated for farther two hours. After completion of the reaction, the reaction solution is cooled and filtrated to provide the title compound as crystal.

Example 87

2-[3-trifluoromethyl-4-(4'-chloro-1-fluoromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 75)

Starting with compound 77, the title compound was synthesized in otherwise a similar manner as Example 68. m.p. 163-164 • C

Example 88

2-[3,5-dichloro-4-(4'-chloro-1-methylthiomethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 96)

In methanol, 2-[3,5-dichloro-4-(4'-chloro-1-chloromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one is reacted with sodium thiomethoxide to provide the title compound.

Example 89

2-[3,5-dichloro-4-(4'-chloro-1-dimethylaminomethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 97)

In dimethylformamide, 2-[3,5-dichloro-4-(4'-chloro-1-chloromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one is reacted with dimethylamine solution.

Example 90

2-[3,5-dichloro-4-(4'-chloro-1-trifluoromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 98)

Starting with 3,5-dichloro-4-(4'-chloro-1-trifluoromethylbenzyl)phenylhydrazine, the title compound is synthesized in otherwise a similar manner as Example 47.

Example 91

2-[3,5-dichloro-4-(4'-chloro-1-hydroxymethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound 99)

Starting with 3,5-dichloro-4-(4'-chloro-1-hydroxymethylbenzyl)phenylhydrazine, the title compound is synthesized in otherwise a similar manner as Example 47.

Example 92

2-[3,5-dichloro-4-(4'-chloro-1-fluoromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 100)

Starting with 2-[3,5-dichloro-4-(4'-chloro-1-hydroxymethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazine-3-one, the title compound is synthesized in otherwise a similar manner as Example 68.

Example 93

2-[3,5-dichloro-4-(4'-chloro-1-chloromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 101)

In toluene, 2-[3,5-dichloro-4-(4'-chloro-1-hydroxymethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one is heated with thionylchloride and purified to give the title compound by a column chromatography.

Example 94

2-[3,5-dichloro-4-(4'-chloro-1-methylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 102)

2-[3,5-dichloro-4-(4'-chloro-1-chloromethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one is dissolved in acetic acid and refluxed with 5-fold molar zinc powder for 3 hours. After concentrated, iced water is added to the results and extracted with ethyl acetate. The extract is dried by $MgSO_4$ and concentrated and purified by a column chromatography to provide the title compound.

Example 95

2-[3,5-dichloro-4-(4'-chloro-1-methoxymethylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (compound No. 103)

In methanol, 2-[3,5-dichloro-4-(4'-chloro-1-chloromethylbenzyl)phenyl]-2,3,4,5-t trahydro-1,2,4-triazin-3-one is reacted with sodium methoxide to provid the titl compound.

Example 96

2-[3-trifluoromethyl-4-(4'-chloro-1-methylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-on (compound No. 104)

In acetic acid is dissolved 2-[3-trifluoromethyl-4-(4'-chloro-1-methylbenzyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-3-one followed by addition of 5-fold molar Zinc powder and refluxed for 3 hours with heated. After adding ice water, the reaction solution is extracted with ethyl acetate. The extract is dried with $MgSO_4$, concentrated and subjected to purification by column chromatography to provide the title compound.

Example 97

2-{4-[2-(4-chlorophenyl)-1-cyanovinyl]-3,5-dichlorophenyl}-4,5-dihydro-1,2,4-triazin-3(2H)-one (compound No. 87)

Starting with 4-[2-(4-chlorophenyl)-1-cyanovinyl]-3,5-dichlorophenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 83-85 °C

H-NMR ($CDCl_3$) δ; 4.12-4.17(2H,J = 2.1Hz,t), 5.83-5.86(1H,J = 2.5Hz,d), 7.07-7.89(8H,m)

Example 98

2-[3,5-dichloro-4-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl-methyl)phenyl]-4,5-dihydro-1,2,4-triazin-3(2H)-one (compound No. 86)

Staring with 3,5-dichloro-4-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl-methyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p 164-165 °C

Example 99

2-[4-(4-chloro-α-chloromethylbenzyl)-3-trifluoromethylphenyl]-4,5-dihydro-1,2,4-triazin-3(2H)-one (compound No.76)

Staring with Compound No.95, the title compound was synthesized in otherwise a similar manner as Example 68. m.p. 157-158 °C

Example 100

2-[3-chloro-4-(4-chloro-α-fluorobenzyl)-5-methylpheyl]-4,5-dihydro-1,2,4-triazin-3(2H)-one (compound No.78)

Staring with Compound No.79, the title compound was synthesized in otherwise a similar manner as Example 68. m.p. 141-142 °C (dec.)

Example 101

2-[3-chloro-4-(4-chloro-α-hydroxybenzyl)-5-methylpheyl]-1,4,5,6-tetrahydro-1,2,4-triazin-3(2H)-one (compound No.80)

Staring with Compound No.81, Compound No.79 was synthesized in otherwise a similar manner as Example 60, followed by additon of excess sodium borate to synthsize compound No. 80. m.p. 146-147 °C

Example 102

2-[3-chloro-4-(4-chlorobenzoyl)-5-methylpheyl]-4.5-dihydro-1,2,4-triazin-3(2H)-one (compound No.81)

Starting with 3-chloro-4-(4-chlorobenzoyl)-5-methylpheylhydrazin , the title compound was synth sized in otherwise a similar manner as Example 47. m.p. 171-172 °C

Example 103

2-[3-chloro-4-(4-chlorobenzoyl)-5-methylpheyl]-1,2,4-triazin-3(2H)-one-5(4H)-thione (compound No.82)

Starting with 2-[3-chloro-4-(4-chlorobenzoyl)-5-methylpheyl]-1,2,4-triazin-3,5(2H,4H)-dione, the title compound was synthesized in otherwise a similar manner as Example 5. m.p. 104-106 • C

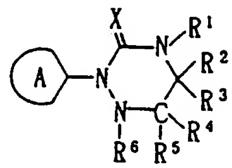
H'-NMR[d6-DMSO] δ; 2.16(3H, s), 7.60 - 7.89 (7H, m), 13.89(1H, br-s).

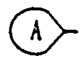
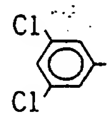
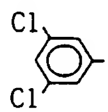
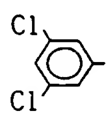
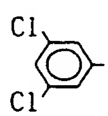
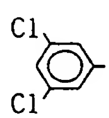
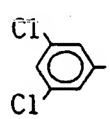
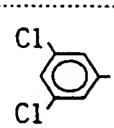
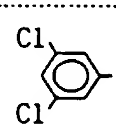
Example 104

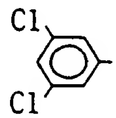
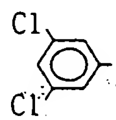
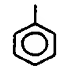
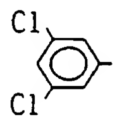
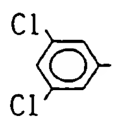
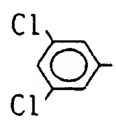
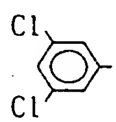
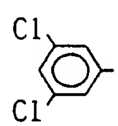
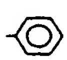
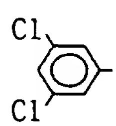
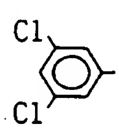
2-[(3-chloro-5-methyl-4-phenyl)phenyl]-4,5-dihydro-1,2,4-triazin-3(2H)-one (compound No. 83)

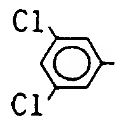
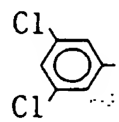
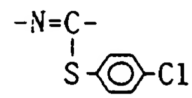
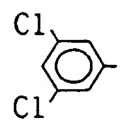
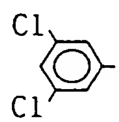
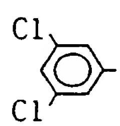
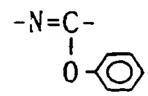
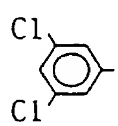
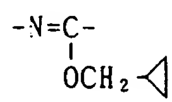
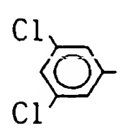
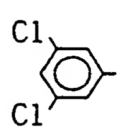
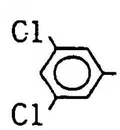
Starting with (3-chloro-5-methyl-4-phenyl)phenylhydrazine, the title compound was synthesized in otherwise a similar manner as Example 47. m.p. 175-176 • C

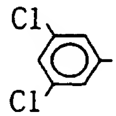
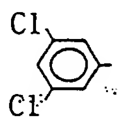
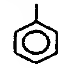
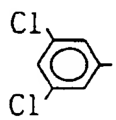
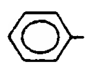
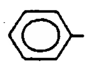
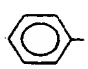
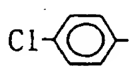
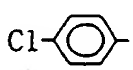
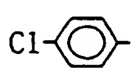
Table 3

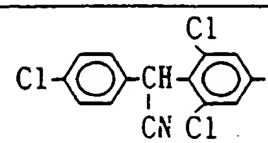
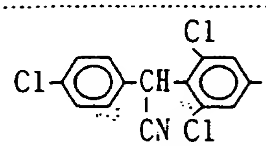
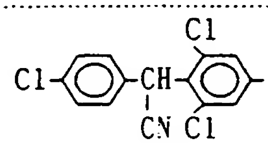
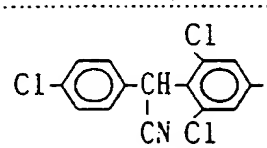
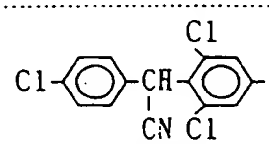
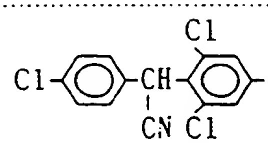
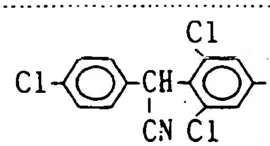
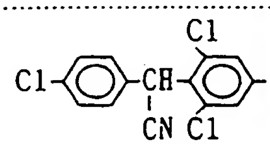
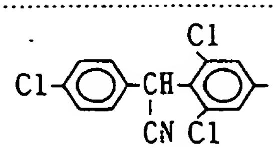


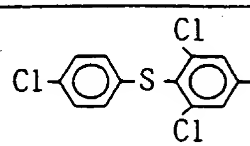
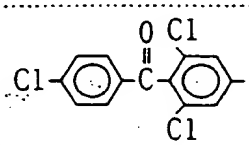
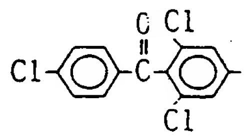
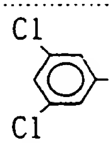
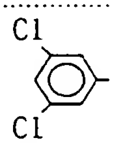
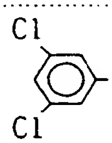
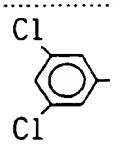
Compound No.		X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
1		O	$-NH-CH_2-$	-N=CH-
2		O	-NH-C(Me)(Me)-	-N=CH-
3		O	-NH-CH(SMe)-	-N=CH-
4		O	-NH-C(SMe)(SMe)-	$-NH-CH_2-$
5		O	$-NH-CH_2-$	$-NH-CH_2-$
6		O	$-NH-CH_2-$	-N=C(Me)-
7		O	-NH-C(=S)-	-N=CH-
8		O	-N(Me)-C(=S)-	$-NH-CH_2-$

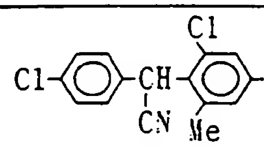
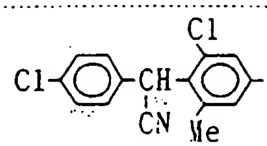
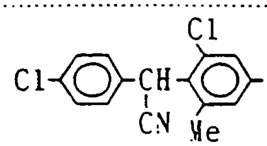
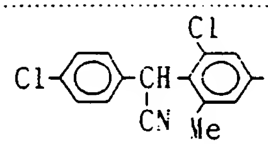
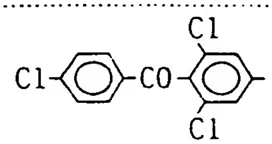
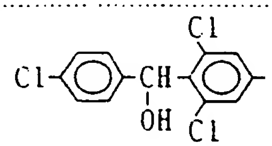
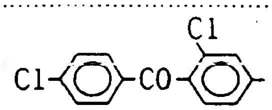
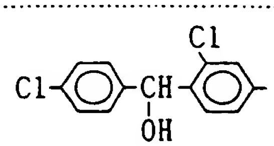
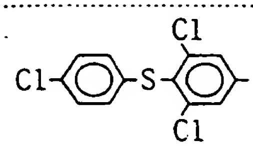
Compound No.	A-	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
9		O	$-NH-C(=S)-$	$-NH-CH_2-$
10		O	-NH-CH- 	$-NH-CH_2-$
11		O	-NH-CH- 	-N=CH-
12		O	$-N(Me)-CH_2-$	$-NH-CH_2-$
13		O	$-NH-CH_2-$	$-NH-CH(Me)-$
14		O	$-N=C(SMe)-$	-N=CH-
15		O	$-N=C(SCH_2-$ $)-$	-N=CH-
16		O	$-N=C(OMe)-$	-N=CH-
17		O	$-N=C(Cl)-$	-N=CH-

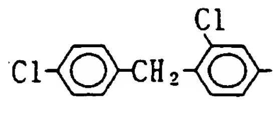
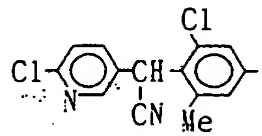
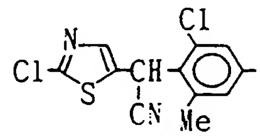
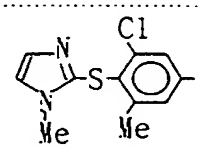
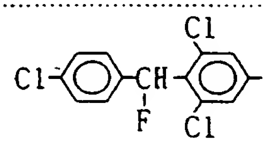
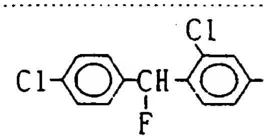
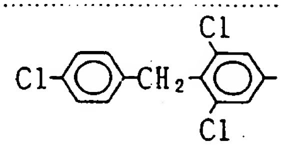
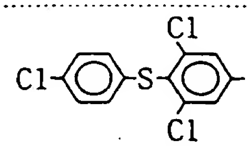
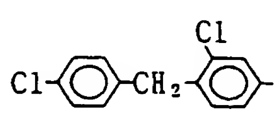
Compound No.	(A)-	X	$-\overset{R^1}{N}-\overset{R^2}{\underset{R^3}{C}}-$	$-\underset{R^6}{N}-\overset{R^5}{\underset{R^4}{C}}-$
18		O	$-N=\underset{F}{C}-$	-N=CH-
19		O		-N=CH-
20		O	$-N=\underset{S-tBu}{C}-$	-N=CH-
21		O	$-N=\underset{O-tBu}{C}-$	-N=CH-
22		O		-N=CH-
23		O		-N=CH-
24		O	$-N=\underset{OCH_2CH_2F}{C}-$	-N=CH-
25		O	$-N=\underset{OCH_2CF_3}{C}-$	-N=CH-
26		O	$-N=\underset{S(CH_2)_3SH}{C}-$	-N=CH-

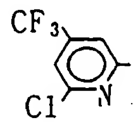
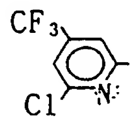
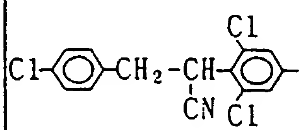
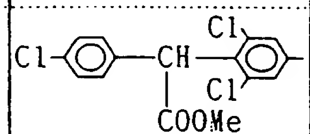
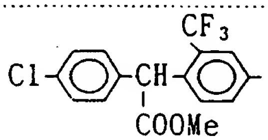
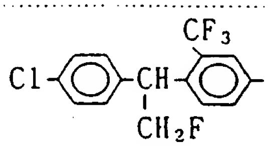
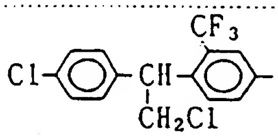
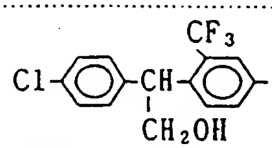
Compound No.	(A)-	X	$-\overset{R^1}{N}-\overset{R^2}{\underset{R^3}{C}}-$	$-\underset{R^6}{N}-\overset{R^5}{\underset{R^4}{C}}-$
27		O	-N=C- 	-N=CH-
28		O	-N=C- 	-N=C- 
29		O	-N=C- SMe	-NH-CH$_2$-
30		O	-NH-C- ‖ S	-N=CH-
31		O	-N=C- SMe	-N=CH-
32		O	-N=C- OMe	-N=CH-
33		O	-NH-C- ‖ S	-N=CH-
34		O	-N=C- SMe	-N=CH-
35		O	-N=C- OMe	-N=CH-

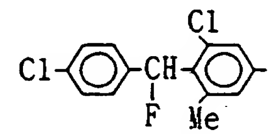
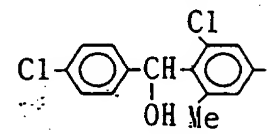
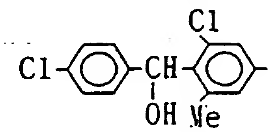
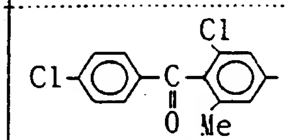
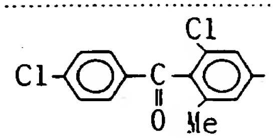
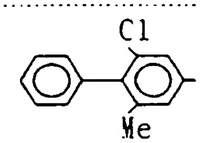
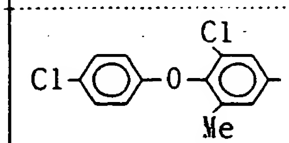
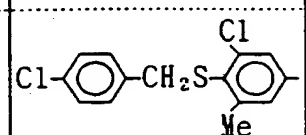
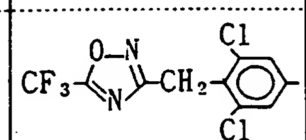
Compound No.	(A)-	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
36		O	$-NH-C(=S)-$	$-N=CH-$
37		O	$-NH-C(=S)-$	$-NH-CH_2-$
38		O	$-NH-CH_2-$	$-NH-CH_2-$
39		O	$-NH-CH_2-$	$-N=C(Me)-$
40		O	$-N(Me)-CH_2-$	$-NH-CH_2-$
41		O	$-NH-CH_2-$	$-N=CH-$
42		O	$-N=C(OMe)-$	$-N=CH-$
43		O	$-N=C(SMe)-$	$-N=CH-$
44		O	$-N=C(Cl)-$	$-N=CH-$

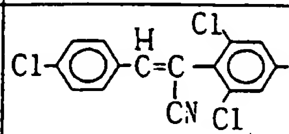
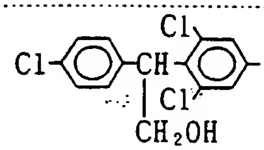
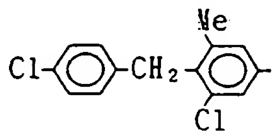
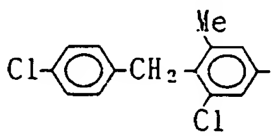
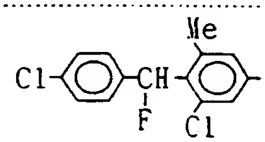
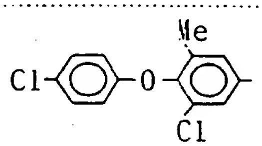
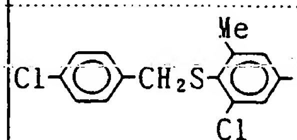
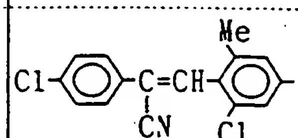
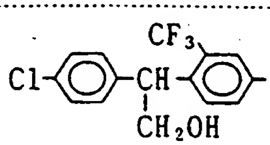
Compound No.	(A)-	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
45		O	$-NH-CH_2-$	$-N=C(Me)-$
46		O	$-NH-CH_2-$	$-N=C(Me)-$
47		O	$-N(COCH_3)-CH_2-$	$-N=C(Me)-$
48		O	$-NH-CH_2-$	$-N(Me)-CH_2-$
49		S	$-NH-CH_2-$	$-N=CH(Cl)-$
50		O	$-NH-CH(Me)-$	$-N(Me)-CH_2-$
51		S	$-NH-CH_2-$	$-N(Me)-CH_2-$

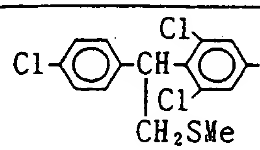
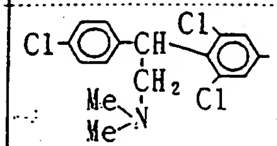
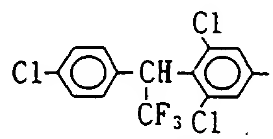
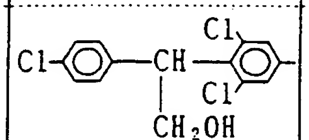
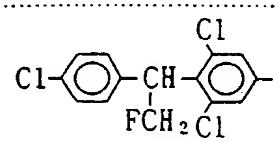
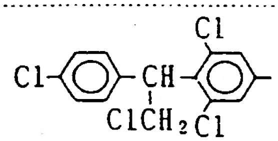
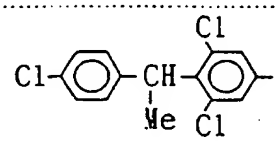
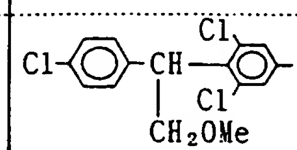
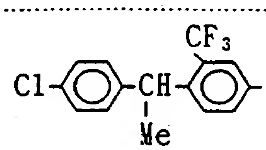
Compound No.	(A)—	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
52		O	$-NH-CH_2-$	$-N=CH-$
53		O	$-NH-CH_2-$	$-NH-CH_2-$
54		O	$-NH-C(=S)-$	$-N=CH-$
55		O	$-NH-C(=S)-$	$-NH-CH_2-$
56		O	$-NH-CH_2-$	$-N=CH-$
57		O	$-NH-CH_2-$	$-N=CH-$
58		O	$-NH-CH_2-$	$-N=CH-$
59		O	$-NH-CH_2-$	$-N=CH-$
60		O	$-NH-CH_2-$	$-N=CH-$

Compound No.	(A)—	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
61		O	$-NH-CH_2-$	$-N=CH-$
62		O	$-NH-CH_2-$	$-N=CH-$
63		O	$-NH-CH_2-$	$-N=CH-$
64		O	$-NH-CH_2-$	$-N=CH-$
65		O	$-NH-CH_2-$	$-N=CH-$
66		O	$-NH-CH_2-$	$-N=CH-$
67		O	$-NH-CH_2-$	$-N=CH-$
68		O	$-NH-CH_2-$	$-NH-CH_2-$
69		O	$-NH-CH_2-$	$-NH-CH_2-$

Compound No.	A	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
70		O	$-NH-CH_2-$	$-N=CH-$
71		O	$-NH-CH_2-$	$-NH-CH_2-$
72		O	$-NH-CH_2-$	$-N=CH-$
73		O	$-NH-CH_2-$	$-N=CH-$
74		O	$-NH-CH_2-$	$-N=CH-$
75		O	$-NH-CH_2-$	$-N=CH-$
76		O	$-NH-CH_2-$	$-N=CH-$
77		O	$-NH-CH_2-$	$-NH-CH_2-$

Compound No.	A	X	$-N(R^1)-C(R^2)(R^3)-$	$-N(R^6)-C(R^5)(R^4)-$
78		O	$-NH-CH_2-$	$-N=CH-$
79		O	$-NH-CH_2-$	$-N=CH-$
80		O	$-NH-CH_2-$	$-N-CH_2-$
81		O	$-NH-CH_2-$	$-N=CH-$
82		O	$-NH-C(=S)-$	$-N=CH-$
83		O	$-NH-CH_2-$	$-N=CH-$
84		O	$-NH-CH_2-$	$-N=CH-$
85		O	$-NH-CH_2-$	$-N=CH-$
86		O	$-NH-CH_2-$	$-N=CH-$

Compound No.	A	X	$-\overset{R^1}{\underset{}{N}}-\overset{R^2}{\underset{R^3}{C}}-$	$-\underset{R^6}{N}-\overset{R^5}{\underset{R^4}{C}}-$
87		O	$-NH-CH_2-$	$-N=CH-$
88		O	$-NH-CH_2-$	$-NH-CH_2-$
89		O	$-NH-CH_2-$	$-N=CH-$
90		O	$-NH-CH_2-$	$-NH-CH_2-$
91		O	$-NH-CH_2-$	$-NH-CH_2$
92		O	$-NH-CH_2-$	$-NH-CH_2-$
93		O	$-NH-CH_2-$	$-NH-CH_2-$
94		O	$-NH-CH_2-$	$-N=CH-$
95		O	$-NH-CH_2-$	$-N=CH-$

Compound No.	(A)–	X	$-\underset{R^1}{N}-\overset{R^2}{\underset{R^3}{C}}-$	$-\underset{R^6}{N}-\overset{R^5}{\underset{R^4}{C}}-$
96		O	-NH-CH$_2$-	-N=CH-
97		O	-NH-CH$_2$-	-N=CH-
98		O	-NH-CH$_2$-	-N=CH-
99		O	-NH-CH$_2$-	-N=CH-
100		O	-NH-CH$_2$-	-N=CH-
101		O	-NH-CH$_2$-	-N=CH-
102		O	-NH-CH$_2$-	-N=CH-
103		O	-NH-CH$_2$-	-N=CH-
104		O	-NH-CH$_2$-	-N=CH-

Formulation Example 1

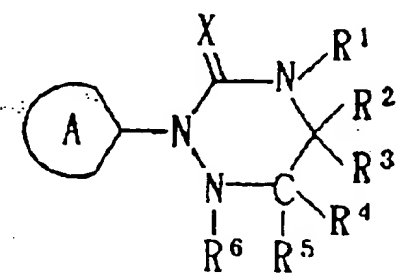
2-(3,5-Dichlorophenyl)-5-methoxy-2,3-dihydro-1,2,4-triazin-3-one (Compound No. 18), 25 g, was pulverized to pass a 355 µm sieve thoroughly and evenly blended with 975 g of defatted rice bran (1:1).

Formulation Example 1

2-(3,5-Dichloroph nyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-one (Compound No. 1), 5.0 g, was dissolv d in 10 cc of methanol, followed by addition of 100 g of soybean. After stirring, the mixtur was dried in vacuo at 50 °C for 10 hours. This mixture was crushed to pass a 500 µm sieve thoroughly and blended uniformly with 895 g of soybean meal to provide a composition.

Claims

1. A compound of the formula:



wherein ring A is an optionally substituted aromatic group;
X is oxygen or sulfur;
R^1 and R^6 are each a hydrogen atom, or a hydrocarbon residue or heterocyclic group which may be bound through a hetero-atom;
R^2 and R^3 are each a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen or sulfur atom, or taken together, represent =S;
R^4 and R^5 are each a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen, nitrogen or sulfur atom;
R^1 and R^2 or R^5 and R^6 together form a chemical bond, provided that where ring A is a phenyl group having at least a halogen atom in position 2 or 4 and X is an oxygen atom, R^5 and R^6 may not bind together to form a chemical bond; or a salt thereof.

2. A compound or a salt thereof as claimed in claim 1, wherein ring A is an optionally substituted phenyl group.

3. A compound or a salt thereof as claimed in claim 1, wherein ring A is an optionally substituted 5- or 6-membered unsaturated heterocyclic group comprising 1 to 4 hetero-atoms selected from oxygen, sulfur or nitrogen.

4. A compound or a salt thereof as claimed in claim 3, wherein said heterocyclic group is a monocyclic heterocyclic group which may be substituted with 1 to 3 substituents.

5. A compound or a salt thereof as claimed in claim 4, wherein ring A is an optionally substituted pyridyl group.

6. A compound or a salt thereof as claimed in claim 1, wherein R^1 is a hydrogen atom or hydrocarbon residue.

7. A compound or a salt thereof as claimed in claim 6, wherein R^1 is an optionally substituted alkyl, aralkyl or aryl group.

8. A compound or a salt thereof as claimed in claim 7, wh r in R^1 is an optionally substituted alkyl.

9. A compound or a salt th r of as claimed in claim 1, wherein R^2 and R^3 are each a hydrogen atom, halogen atom, an optionally substituted C_{1-4} alkyl, C_{1-4} alkoxy, ph noxy, C_{1-4} alkylthio or phenylthio group, or taken together, r present =S.

10. A compound or a salt ther of as claimed in claim 9, wherein R^2 and R^3 are each a hydrogen atom or an optionally substituted C_{1-4} alkyl.

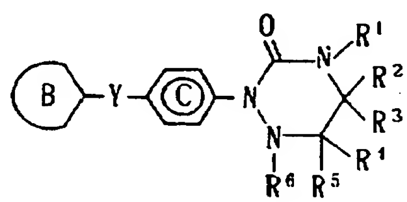
11. A compound or a salt thereof as claimed in claim 9, wherein R^2 and R^3 taken together represent =S.

12. A compound or a salt thereof as claimed in claim 1, wherein R^4 and R^5 are each a hydrogen atom, halogen atom or an optionally substituted alkyl or aryl group.

13. A compound or a salt thereof as claimed in claim 12, wherein R^4 and R^5 are each a hydrogen atom, halogen atom or C_{1-4} alkyl.

14. A compound or a salt thereof as claimed in claim 1, wherein R^6 is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group.

15. A compound or a salt thereof as claimed in claim 1, wherein said compound has a structure of the formula:



wherein ring B is an optionally substituted 5- or 6-membered cyclic group which may contain one or more hetero-atoms;
ring C is an optionally substituted phenylene group;
R^1 and R^6 are each a hydrogen atom, or a hydrocarbon residue or heterocyclic group which may be bound through a hetero-atom;
R^2 and R^3 are each a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen or sulfur atom, or taken together, represent =S;
R^4 and R^5 are each a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen, nitrogen or sulfur atom;
R^1 and R^2 or R^5 and R^6 together form a chemical bond;
Y is a chemical bond, -O-, -S(O)$_m$-, or a optionally substituted lower hydrocarbon residue; and m is 0, 1 or 2.

16. A compound or a salt thereof as claimed in claim 15, wherein the ring B is an optionally substituted phenyl, pyridyl, thiazolyl or imidazolyl group.

17. A compound or a salt thereof as claimed in claim, wherein the ring B is an optionally substituted phenyl group.

18. A compound or a salt thereof as claimed in claim 15, wherein R^1 and R^6 are each hydrogen or a hydrocarbon residue.

19. A compound or a salt thereof as claimed in claim 18, wherein R^1 is hydrogen or an optionally substituted alkyl group.

20. A compound or a salt th r of as claimed in claim 18, wherein R^1 is an acyl group.

21. A compound or a salt ther of as claimed in claim 15, wherein R^2 and R^3 are each a hydrogen atom, halogen atom, an optionally substitued alkyl, alkoxy or C_{1-4} alkylthio group, or tog ther, represent = S.

22. A compound or a salt thereof as claimed in claim 21, wherein R^2 and R^3 are both hydrogen atoms.

23. A compound or a salt thereof as claimed in claim 15, wherein R^4 and R^5 are each a hydrogen atom, halogen atom, an optionally substitut d alkyl or phenyl group.

24. A compound or a salt ther of as claimed in claim 15, wherein Y is an optionally substituted divalent C_{1-4} hydrocarbon group.

25. A compound or a salt thereof as claimed in claim 18, wherein R^6 is hydrogen or an optionally substituted alkyl group.

26. A compound or a salt thereof as claimed in claim 18, wherein R^6 is an acyl group.

27. An antiprotozoan composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient or diluent.

28. The composition as claimed in claim 27, wherein said protozoa is coccidia.

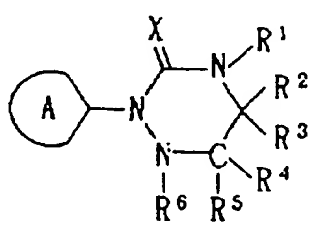
29. An animal feed additive premix comprising a compound according to claim 1 or a physiologically acceptable salt thereof.

30. A method for inhibiting protozoa in an animal which comprises administering an effective amount of the compound according to claim 1 or a physiologically acceptable salt thereof to said animal.

31. The method as claimed in claim 30, wherein said animal is a bird.

32. A method for breeding an animal which comprises administering the compound according to claim 1 or a physiologically acceptable salt thereof to said animal.

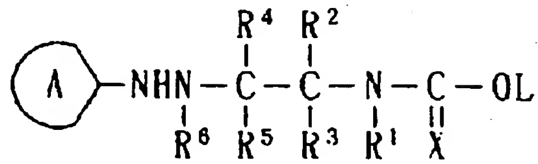
33. A method for preparing a compound of the formula:



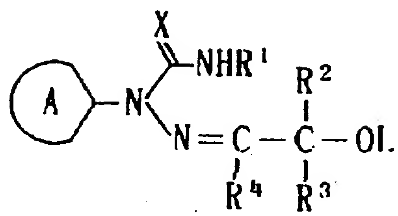
wherein ring A is an optionally substituted aromatic group;
X is oxygen or sulfur;
R^1 and R^6 are each a hydrogen atom, or a hydrocarbon residue or heterocyclic group which may be bound through a hetero-atom;
R^2 and R^3 are each a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen or sulfur atom, or taken together, represent =S;
R^4 and R^5 are each a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen, nitrogen or sulfur atom;
R^1 and R^2 or R^5 and R^6 together form a chemical bond, provided that where ring A is a phenyl group having at least a halogen atom in position 2 or -4 and X is oxygen atom, R^5 and R^6, may not bind together to form a chemical bond.

34. A method as claimed in claim 33, which comprises cyclizing the compound of the formula:

a)

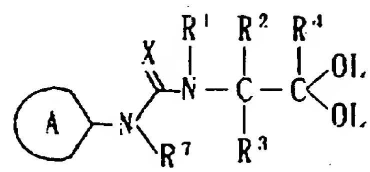


b)



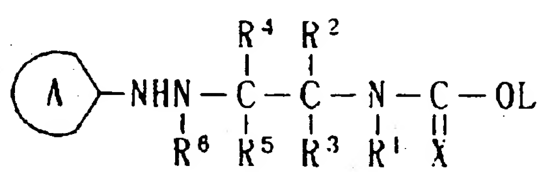
or

c)

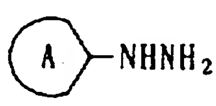


wherein A, R^1, R^2, R^3, R^4, R^5 and R^6 are of the same meaning defined in claim 27, R^7 is an optionally protected amino group and L is an alkyl or acyl.

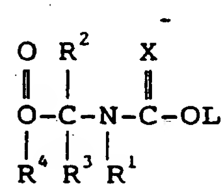
35. A method for preparing a compound of the formula:



which comprises reacting the compound of the formula:



with the compound of the formula:



wherein A, R^1, R^2, R^3, R^4 and X are as defined in claim 1 and L is alkyl or aryl.

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European Patent Office
Office européen des brevets

(11) Publication number: **0 648 760 A3**

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19.04.95 Bulletin 95/16

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28.06.95 Bulletin 95/26

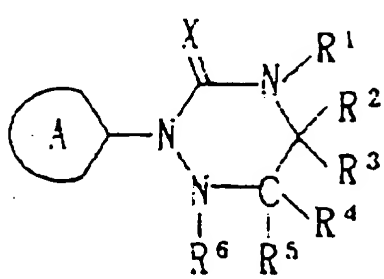
(71) Applicant: **TAKEDA CHEMICAL INDUSTRIES, LTD.**
1-1, Doshomachi 4-chome
Chuo-ku,
Osaka 541 (JP)

(72) Inventor: **Miki, Hideki**
23-14, Shinkofudai 2-chome,
Toyono-cho
Toyone-gun,
Osaka 563-01 (JP)
Inventor: **Iwanaga, Koichi**
201-1-5, Fushiodai 5-chome
Ikeda,
Osaka 563 (JP)
Inventor: **Matsuno, Toshimi**
14-9-1103, Niitaka 6-chome
Yodogawa-ku,
Osaka 532 (JP)

(74) Representative: **Fürniss, Peter, Dr.**
Kuhnen, Wacker & Partner
Alois-Steinecker-Strasse 22
D-85354 Freising (DE)

(54) **Triazine derivative, production and use thereof.**

(57) The present invention provides a novel triazine derivative of the formula



wherein ring A is an optionally substituted aromatic group which be;

X is an oxygen or sulfur atom;

R^1 and R^6 are each a hydrogen atom or an optionally substituted hydrocarbon residue or heterocyclic group which may bound through a heteroatom;

R^2 and R^3 are each independently a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen or sulfur atom, or taken together, represent =S;

R^4 and R^5 are each independently a hydrogen atom, a halogen atom, or a group bound through a carbon, oxygen, nitrogen or sulfur atom;

R^1 and R^2, and R^5 and R^6, may each bind together to form a ch mical bond; provided that wh r ring A is a phenyl group having at least a halogen atom in position-2 or 4 and X is an oxygen atom, R^4 and R^5 do not conjoinedly represent a ch mical bond and an antiprotozoan composition containing the sam or salt thereof.

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number
EP 94 11 6173

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP-A-0 457 015 (BAYER AG) 21 November 1991	1,2, 15-17, 24,27, 28,33,34	C07D401/10 C07D417/10 C07D403/12 C07D401/04 C07D413/10 C07D253/07 C07D253/06 C07D253/075 A61K31/53
	especially when R3 is H		
Y	* the whole document *	1-29,33, 34	

D,X	EP-A-0 476 439 (BAYER AG) 25 March 1992	1,2, 15-17, 24,27, 28,33,34	
	especially when R5=H		
Y	* the whole document *	1-29,33, 34	

	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

~~Claims searched completely :~~

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	19 December 1994	Scruton-Evans, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
 : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 94 11 6173

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP-A-0 383 285 (HOECHST AG) 22 August 1990	1,2, 12-16, 23,27, 28,33	
	especially when R4=H		
Y	* the whole document *	1-29,33, 34	

X	GB-A-1 562 935 (HOECHST AG) 19 March 1980	1,2,14, 27,28, 33,34	
Y	* the whole document *	1-29,33, 34	
	---		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	DE-A-25 32 363 (BAYER AG) 3 February 1977	1,2, 15-17, 27,28, 33,34	
Y	* the whole document *	1-29,33, 34	

X	US-A-4 631 278 (G.M.BOECKX) 23 December 1986	1,2, 15-17, 24,27, 28,33,34	
Y	* the whole document *	1-29,33, 34	

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EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 94 11 6173

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D,X	J. MED. CHEM., vol.22, no.12, 1979 pages 1483 - 1487 M.W.MILLER ET AL 'Anticoccidial derivatives of 6-Azauracil' *see whole document and especially Table I*	1-4,6, 27-29	
Y		1-29,33, 34	
X	WO-A-86 00072 (FMC CORPORATION) 3 January 1986 * the whole document *	1,2,33, 34	
X	SYNTHETIC COMMUNICATIONS, vol.21, no.15, 1991 pages 1695 - 1703 J DANIEL ET AL 'Cyclisation of chlorosulfonyl isocyanate with phenylhydrazones' *see compounds 6a-6c*	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	INDIAN JOURNAL OF HETEROCYCLIC CHEMISTRY, vol.3, October 1993 pages 121 - 126 R.M.ABDEL-RAHMAN ET AL 'Synthesis and biological activity of some new heterocyclic systems' *see compound XIV*	1,3	
X	TETRAHEDRON, vol.48, no.42, 1992 pages 9295 - 9304 A.ELGHANDOUR ET AL 'Studies with polyfunctionally substituted heteroaromatics' *see compound 13*	1,2	

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 94 11 6173

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	JUSTUS LIEBIG ANN. CHEM., vol.12, 1978 pages 2033 - 2043 H.GNICHTEL 'Isomere Heterocyclen durch Cyclisierung von syn- und anti- alpha Aminohydrazonen' *see compounds 4a and 4b*	1,2	
X	JUSTUS LIEBIG ANN. CHEM., vol.713, 1968 pages 151 - 161 A.MUSTAFA ET AL 'Das Verhalten von Oxazolinonen-(5) und Thiazolinonen-(5) gegen N-Phenyl-hydroxylamin und Phenylhydrazin' *see compound 20c*	1,2	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,

namely:

see sheet -B-

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respects of which search fees have been paid,

namely claims:

☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims: 1-29,33,34

European Patent
Office

EP 94 11 6173 -B-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

1. Claims 1-29,33,34
2. Claim 35: This claim is an independent claim for a process which has no relationship to the end products of claim 1, and has no technical parameters

EP 94 11 6173

-C-

Although all of the claims 1-29,33,34 have been searched, it is not possible to cite all of the X documents found, as the possibility of R^3 being -OH with R^1 and R^2 as a double bond is included within the claim, and this is the tantomeric form of the widely known 3,5 diones (see description, page 18, line 5).
Also, the broad terms "group bound through C,O,N,S", "hydrocarbon residue", "optionally substituted", etc. encompass very many known compounds.